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PANEL DISCUSSION ON THE PALLIATION OF ADVANCED CANCER IN THE OLDER AGE GROUPS*

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MODERATOR SLAUGHTER: Cancer is by no means confined to older age groups. The majority of cases occur in elderly people.

If we could utilize known methods of cancer treatment to the best of our ability, the cure rate might approach 50 to 75 per cent. In actual practice, probably less than 25 per cent of cancer patients, excluding those with carcinoma of the skin and lip, are cured by modern methods of treatment. That figure points up the statistical enormity of the problem of patients who are not cured but who seek palliation. It is the concern of physicians to do everything possible for these patients and not to ignore them.

Among several means of treatment are palliative surgery, which is important in relation to the cancer problem, and palliative irradiation. Perhaps even more important for the future are newer approaches, such as endocrine modification and chemotherapy. These means are being used more and more. I hope that they will become increasingly useful in the management of cancer.

Cancer affects every tissue in the body. Almost every medical specialty is involved. Therefore, deliberately included in this panel were a general surgeon, a gynecologist with extensive experience in radiation therapy of the pelvic organs, an internist-endocrinologist, and a radiologist. I should like to hear from each of them.

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First, I shall ask Dr. Eugene M. Bricker, a general surgeon, to discuss the palliative surgical management of carcinoma. Dr. Bricker.

DR. BRICKER: Dr. Slaughter, I should like to say that, although my subject for discussion is palliative surgery for carcinoma in the older age group, we need not confine our thoughts to the elderly, because cancer surgery in them differs little from cancer surgery in general.

Known for several years, but recently emphasized by Gilchrist, DePeyster, Moyer and Key, is the fact that the mortality rate among patients past the age of 70 years undergoing surgery for carcinoma does not exceed appreciably the mortality rate for patients under 70 years of age undergoing similar surgery. Therefore, statements about palliation may apply to persons of all ages, although more cancer is found in older people.

The best palliation for cancer in young and old, with few exceptions, is attempted removal of the lesion in the hope that it will prove curative. In the older person, debilitation because of repeated myocardial infarctions, uncontrolled cardiac failure, or the presence of malignant hypertension of an advanced degree are the most noteworthy findings that contraindicate surgery or necessitate an altered surgical approach.

In attempting palliation for inoperable, incurable lesions, our aim is to keep the patient as comfortable as possible for as long as possible. Usually this means relieving pain and the physio-pathologic effects of the advanced growth. These effects may be an obstruction of one of the body tubes, hemorrhage, extensive sloughing, or fistulae. Our plan, then, must provide for the control of pain, obstruction, hemorrhage, fistulae, and sepsis. How can this be accomplished? What surgical methods are at hand? The procedure may be an amputative or an extirpative one. In the case of an advanced, incurable lesion of an extremity resulting in disability from pain and sloughing, amputation should be of great benefit to the patient. A tumor within the abdomen may be removed because of distressing symptoms, even though a cure cannot be expected. The palliative attempt may be made by means of a decompressing or short-circuiting procedure applied to an obstruction of one of the various body tubes; this provides relief from the distressing effects of the tumor, even though it is not feasible to attack the growth directly. A final method of approach for palliation is a direct attack upon the nervous system in order to free the patient of the sensation of pain caused by the tumor.

As a further example of amputative and extirpative surgery, one can point to amputation for advanced cancer of an extremity. Advanced carcinoma of the breast may occasionally lend itself to amputation as a palliative measure, though this is a more debatable example.

Carcinoma of the bowel (from the stomach to the colon) frequently calls for palliative resection. However, the results seem to be more gratifying in advanced neoplasms of the colon rather than of the stomach or other upper abdominal viscera. In the case of cancer of the colon associated with liver metastases, most surgeons believe the best palliation is achieved by removing the tumor and reestablishing the continuity of the gastro-intestinal tract. This approach is less

successful when applied to carcinoma of the stomach with liver metastases. Each lesion should be individualized and treated accordingly. If resection will relieve obstruction, and if gastro-intestinal continuity can be restored, some degree of palliation will have been achieved. The same statement might apply to carcinoma of the esophagus.

As an example of a decompressing and by-passing operation, gastro-enterostomy has proved a boon to many patients. Although advanced carcinoma of the stomach does not usually lend itself well to resection, it may be possible to achieve excellent palliation if the obstruction can be relieved by a simple by-pass procedure. The same approach can be applied to the small intestine and colon. Colostomy is another type of by-pass operation particularly applicable to obstructing carcinoma of the left colon and rectum.

In the case of carcinoma of the head of the pancreas and bile ducts, palliation with the relief of jaundice is achieved through decompression, using the gallbladder or the common duct for anastomosis to the intestine.

I should like to comment briefly on pelvic exenteration as a palliative procedure. We have found that older people tolerate this operation well. Indeed, we frequently favor exenteration in older people even though a lesser procedure might suffice. Our reason for this choice was the unexpectedly low incidence of urinary complications following transplantation of the ureters to an isolated ileal segment, as compared to the incidence of such complications following partial pelvic exenteration with preservation of the urinary bladder.

The foregoing are some of the points with regard to the general surgical approach to palliation. When there is nothing further to offer the patient from this direction, a neurosurgical procedure such as rhizotomy, chordotomy, or lobotomy may effectively relieve pain. The selection of the patient in whom such an operation might be feasible requires the exercise of keen judgment. The problem is to determine whether the additional length of survival and the chances of benefit from further surgery are great enough to justify the operation. The prospect of another operation is very distressing for a patient in the terminal stages who has already suffered a great deal. For this reason, neurosurgical procedures should be applied with great care and discrimination. When so applied, they may greatly alleviate the terminal distress of the cancer patient.

MODERATOR SLAUGHTER: Thank you, Dr. Bricker.

It might be well now to hear Dr. Erich M. Uhlmann, a radiologist. Dr. Uhlmann.

DR. UHLMANN: Radiation therapy per se is not an anesthetic and is not primarily a pain killer. In the opinion of many members of the medical profession, this branch of medicine deserves little credit and is blamed for almost everything that may happen to a patient, such as burns, edema, malignant growths, fractures and, in one instance in my experience, even pregnancy.

In discussing this subject, we must consider two aspects—the perception of pain and the reaction to pain. The latter depends to a great extent upon the emotional status of the patient. Pain associated with cancer differs in quality, in severity, and in duration. It can be superficial, deep, or referred, but is seldom

central. There is no objective way to measure the intensity of pain. Unfortunately, when a pain-killing procedure, including the utilization of radiation therapy, might serve its purpose best for cancer patients, it is seldom needed. As a rule, primary carcinoma does not produce pain in its early stages. That is one of the reasons why patients do not seek consultation in the initial stages of the disease. Some malignant neoplasms are excepted from this general rule. Carcinomas of the pancreas or gallbladder may produce early pain but these tumors do not lend themselves readily to the influence of radiation therapy. In any event, such therapy can not be considered before a definite diagnosis has been established, for which laparotomy must be performed. Pain in some primary tumors, *e.g.*, sarcoma of bone, is relieved following radiation therapy. However, subjective symptoms often develop only in the advanced stage of the disease. Pain associated with so-called Ewing's tumor of bone can readily be influenced by irradiation, but in other tumors like multiple myeloma, the response is much less favorable.

Pain in metastatic malignant conditions may be variously described as discomfort, aches, suffering, or agony. Often the pain is not due to the tumor itself, but to its sequelae produced by pressure on nerves or other organs. Radiation therapy frequently is helpful in such instances and sometimes offers dramatic relief. A favorable response does not necessarily depend upon the sensitivity of the primary lesion to irradiation. As an example, radiation therapy may fail to exert any influence on a certain type of carcinoma of the breast. However, the metastases to bone produced by the same breast cancer may respond readily. Often, the response is expressed not only in the relief of subjective symptoms, but in demonstrable recalcification of destroyed bone tissue. In some instances, even pathologic fractures caused by tumor growth may heal following radiation therapy. Squamous-cell carcinoma of the lung, the so-called oat-cell type of bronchogenic carcinoma, often produces bony metastases that are readily influenced by radiation therapy. Skeletal metastases following primary carcinoma of the thyroid also respond favorably to irradiation. The results are less favorable in treating metastases of primary carcinomas of the gastro-intestinal tract, the kidneys, and the prostate.

Lesions often benefited by irradiation are the leukemias, Hodgkin's disease, and lymphosarcomas. Pain due to obstruction and pressure in the abdomen or retroperitoneal space, mediastinal masses, and the spleen in leukemia may be relieved following radiation therapy. Some patients have pain due to an accumulation of fluid in the body cavities specifically in the chest or abdomen. Pressure of fluid in the thoracic cage frequently produces coughing and pain. Primary and secondary tumors of the ovaries are often associated with large amounts of ascitic fluid which causes pressure on the lymphatics and blood vessels, resulting in edema of the lower extremities. Properly executed radiation therapy can diminish the accumulation of fluid and often suppress it completely, with resultant relief of pain.

Occasionally, pain due to carcinoma of the pancreas, liver, or stomach can be relieved by relatively small amounts of radiation. In many instances of car-

cinoma of the sigmoid with metastases to the area of the sacral plexus, radiation therapy relieves the subjective symptoms. In a similar manner, large mediastinal masses causing compression of the superior vena cava and subsequent dilatation of blood vessels in the head and neck may subside following radiation therapy, with consequent relief of discomfort. No great benefit can be expected from treatment of extensive carcinomas of the gastro-intestinal tract, and seldom can palliation be achieved in carcinoma of the urinary bladder. The amount of radiation necessary to treat the latter lesion successfully is so great that irritation of the mucous membrane of the bladder is unavoidable. This form of treatment, therefore, is not advocated for tumors in this location.

In summary, the best results from radiation therapy can be expected in metastatic lesions to the skeletal system and in certain primary bone tumors. The relief of pain in such instances is often dramatic and lasting.

MODERATOR SLAUGHTER: Thank you, Dr. Uhlmann.

Now, I shall call on Dr. Samuel G. Taylor, an internist. Dr. Taylor.

DR. TAYLOR: I shall briefly review other measures available for the treatment of disseminated cancer, limiting my remarks to chemotherapy and endocrine alterations in the treatment of solid tumors in the aged.

Although great advances have been made with antimetabolites and other chemotherapeutic agents in the treatment of blood dyscrasias, the use of these agents in treating solid malignant tumors has been disappointing to date, with the outstanding exception of the nitrogen mustards in treatment of the lymphomatous group of tumors. Temporary regression of any tumor may also be accomplished, if the mustard can be injected into the afferent circulation in such a way that a high concentration of the drug can reach the tumor without going into the general circulation in toxic doses. Thus nitrogen mustard injected into the cubital vein may cause some regression of pulmonary lesions, and injected by catheter into the hepatic artery may produce regression of liver metastases. Intracavitary injections of alkylating agents such as nitrogen mustard or thio-TEPA may be effective in reducing the accumulation of fluid. For the treatment of generalized metastases, these agents are of no practical value, and their use usually results in further debility of the patient due to depression of the bone marrow. Injections of thio-TEPA directly into the tumor have been recommended by one author, but little palliation is achieved by merely sclerosing the local tumor when the disability is due to generalized disease. More effective agents will have to be developed before satisfactory chemotherapy of cancer becomes clinically worth while.

Therapeutic alterations in endocrine balance may result in significant, though temporary, regression of the tumor in about 50 per cent of aged patients with mammary cancer and in about 70 per cent of patients with prostatic cancer. Large doses of estrogen should be the first endocrine therapy in a case of disseminated breast cancer in a woman three or more years after the menopause. The greater the time since the menopause, the greater the likelihood of a favorable response. Should estrogens not be effective in producing regression of the tumor in four to six seeks, androgen therapy should be tried. Rarely, oophorectomy may be of value, should the vaginal smear suggest estrogenic activity.

When the usefulness of these forms of therapy has ended, there are certain selected cases in which further regression of the tumor may be obtained by adrenalectomy or hypophysectomy.

Estrogen should be given in a dosage equivalent to 15 mg. of diethylstilbestrol a day. Androgens should be given as testosterone propionate, 50 to 100 mg. three times a week, or its equivalent. The weaker androgens offer no advantage, as suppression of the tumor apparently depends upon the androgenicity of the drug.

Carcinoma of the male breast is more frequently controlled with estrogen therapy or castration, and usually for longer periods of time, than is carcinoma of the female breast. Adrenalectomy may extend palliation when the tumor is reactivated.

Surgical castration offers the best form of therapy in cancer of the prostate, although administration of diethylstilbestrol or other estrogens is also effective. Other ablative procedures such as adrenalectomy and hypophysectomy, though they may be temporarily effective, are seldom worth while because of the short-lived regression produced.

Cortisone and hydrocortisone, and their analogs prednisone and prednisolone, are effective in controlling tumor growth and producing satisfactory, though temporary, regression of tumors in the lymphoma group. These drugs can be used as the only form of therapy, or in conjunction with radiation or nitrogen mustard. Not infrequently, when radiation is no longer effective, and mustards have been given to the maximum tolerance of the patient, corticoid therapy may produce an additional, though temporary, regression of the disease. Although treatment with prednisone or prednisolone gives rise to the same problems of abnormal fat deposits, moon facies, hirsutism and carbohydrate alterations as does treatment with cortisone or hydrocortisone, disturbances of electrolyte metabolism are less common. The effect of these analogs, therefore, is superior to that of the natural hormones. The most serious complication attendant upon the use of corticoids is the frequent development of gastric and duodenal ulcers. We have thought that we have been able frequently to prevent this complication by the use of modified ulcer management.

Although actual regression of other than lymphomatous types of tumor rarely occurs during corticoid therapy, these drugs offer great palliation by reducing the inflammatory reaction and edema around the infiltrating tumor, and hence reducing pain. Probably by the same mechanism, neurologic alterations produced by cerebral metastases may be completely controlled for periods of many months by the use of 50 to 100 mg. of prednisone or prednisolone daily. Visual disturbances, paralyses, convulsions, and paresthesias caused by intracranial lesions may disappear during prednisone or prednisolone therapy in large dosages. As the disease progresses, the dosage of prednisone necessary to control the symptoms may have to be increased. The corticoids are also of value in cases of hypercalcemia caused by rapid progression of osseous metastases. The mechanism is not understood.

MODERATOR SLAUGHTER: Thank you, Dr. Taylor.

Next we shall hear Dr. Herbert Schmitz, a gynecologist. Dr. Schmitz.

DR. SCHMITZ: I shall concentrate my remarks on pelvic malignancies because I have confined myself to work in this field.

Surgical attempts at palliation to lessen pain and obstruction have a sound foundation, as does irradiation of the patient not only for primary treatment of the malignant condition, but also for palliation. In gynecology, we have a wealth of material, because over 60 per cent of malignant tumors originate in the breast and pelvis of the female. The survival rate is not good. For instance, in the case of carcinoma of the cervix, under ideal conditions we can salvage from 40 to 50 per cent of patients for longer than five years. In carcinoma of the fundus, we can do better in cases of early extension of the disease, but the over-all salvage rate is unsatisfactory, being in the neighborhood of 50 to 55 per cent. In carcinoma of the ovary, the salvage rate drops to about 20 to 22 per cent because of the delay in treatment. In carcinoma of the vulva, the rate had remained stationary at approximately 20 per cent for years; with improved and more extensive surgery, it has now been raised to 50 per cent. Thus, about 50 per cent of all patients seen will be candidates for palliation.

The groups of patients to be discussed are those who have had primary therapy by irradiation, surgical procedures, or a combination of both and have active disease with resulting discomfort. They are for the most part in the upper age-bracket, because gynecologic cancer is more often found in women from 50 to 70 years of age.

These means having been tried, the patient is in a position where no further definitive surgical treatment is available, and no further irradiation indicated except as a palliative measure. That is, the patient is in Group IV. I dislike the use of the word "terminal" to describe the patient with advanced carcinoma, because it implies subsequent removal to a nursing home under narcotic therapy.

Many people will say that nothing can be done for such a woman, except to administer opiates for the relief of pain. We must remember that studies show definitely that the average life of the Group IV gynecologic patient is about fourteen months. That means there are fourteen months in which to treat the patient, because she must not be forgotten. If treatment with opiates is commenced too soon; the patient is likely to become addicted, and that presents a problem to everyone.

As I see it, there has to be a definite plan which must be followed meticuously, so that the patient is given something to depend upon. The first thing is to prepare her by an almost perfect doctor-patient relationship. She is in a dilemma and must have someone to whom she can turn and be assured that she will not be permitted to suffer, and that nothing will be neglected. She has to have someone she knows has an interest in her and will see her in this trying period and keep her as comfortable as possible. The next thing is that she must be kept psychologically prepared; and here you may have to have a spiritual adviser. It is important to keep these patients mentally alert. Then, such things as radiation therapy and chemotherapeutic agents may be used for palliation. She must know that she is not going to be relegated to a corner. I am thinking of the great Jesuit from St.

Louis University who for seven years suffered from carcinoma of the bladder and finally had extensive pulmonary metastases. The patient knew he had carcinoma of the bladder because a growth had been fulgurated there on numerous occasions. He preferred to continue working. Finally when he had hematuria and pain, he commented, "Thank God, I had all these years to put my thinking into shape. I had plenty of time to prepare to go."

Yesterday, I listened to a discussion by a learned internist in St. Louis. He allowed that everyone could live ten years longer by observing certain rules—keeping occupied, avoiding worry, and avoiding fats. Among the things enumerated, he said that it was most important to have an objective and a hobby, and to do something every day with someone else—in other words, to maintain an interest.

When pain develops in a patient with a malignant growth in the pelvis, one of three things has happened: 1) obstruction or infection, or both, in the urinary tract, 2) pyometra or hematometra, or 3) extension of the disease into the large nerves, or pressure of the growth on nerve tissue. Pyometra is treated by dilating the cervix and leaving a rubber drain in place.

Hydroureter is relieved for as long a time as possible by the use of catheters. For deep sacral pain, subarachnoid injections of alcohol usually control the discomfort.

Complications must be combated as they arise. Probably the most common are repeated hemorrhage and a foul discharge. The discharge can be treated with certain types of douches, by cauterization and cleaning of the area, or by the use of acetone packs. The latter is an old treatment handed down to me by my father; he used acetone to fix fungating lesions, and thereafter the discharge lessened. If the patient returns, treatment is repeated. In a patient with fistulae, colostomy, as Dr. Bricker brought out, affords great relief. It is preferable to have feces discharged by this route, than uncontrolled through the rectum.

Frequently, breakdown of tissue occurs from ischemia, and fistulae form in the urinary tract. This is the only circumstance in which I fit a patient with a diaphragm; it is necessary in a woman with a vesicovaginal fistula. The patient can be kept fairly dry in this manner.

MODERATOR SLAUGHTER: Thank you, Dr. Schmitz.

There is so much variation in treatment for cancer of the breast that I should like to ask each panel member the chronologic order in which he employs the various methods. Dr. Bricker, what is your custom in handling cases of breast cancer, that is, both cured and uncured lesions?

DR. BRICKER: If localized to the skin, metastases may possibly be controlled by irradiation alone, but consideration should also be given to oophorectomy or to irradiation of the ovaries. In other words, the initial attack upon the incurable lesion is through irradiation, and in premenopausal patients castration is added. Such treatment may control the disease for months or years. With further evidence of recurrence, a response can be expected from the use of hormones. In the premenopausal patient, I would use testosterone. In the post-

menopausal patient, when the recurrence is not in bone, I would use estrogen. When there is bony involvement, I would start testosterone in the postmenopausal patient. Patients with local lesions amenable to radiation therapy must be separated from others; and a search should be made for patients who might conceivably be benefited by adrenalectomy. I do not perform adrenalectomy because I have not had good results with it. This procedure is sometimes carried out, however, and the big problem is when to advise that a patient have it.

DR. TAYLOR: I take exception to the remark that osseous metastases are an indication for the use of androgens instead of estrogens. In an analysis of 1,005 cases in a cooperative study of the American Medical Association, a higher percentage of osseous regressions occurred from the use of estrogens than from the use of androgens. The impression that androgens are superior is a common fallacy.

MODERATOR SLAUGHTER: That is what was found in your study too, isn't it?

DR. TAYLOR: Yes.

MODERATOR SLAUGHTER: This information from Dr. Taylor is not published as yet, but is about to be, so that it is new.

Dr. Schmitz, you certainly have removed more ovaries than any of us. What is your concept of the chronologic order of treatment in breast cancer, particularly of routine castration? That might be of interest.

DR. SCHMITZ: We must not forget in this discussion that many patients with what is thought to be terminal carcinoma live for years. In other words, we know nothing as to which patient with a particular tumor is going to survive. Therefore, I believe that treatment is justified in every patient. There should not be a hopeless situation in which the patient is refused treatment.

I think first of definitive treatment and then of palliative therapy. Let us call the rest psychotherapy; some patients are benefited because of what we do for them.

In carcinoma of the breast, we have not favored routine castration. Patients are treated for early lesions by radical mastectomy. In our institution, they receive deep roentgen-ray therapy. If the disease recurs, whether it be osseous or local recurrence, oophorectomy is performed. Then, hormonal therapy may be of benefit. Finally, we subject the patient to adrenalectomy or, of late, hypophysectomy.

MODERATOR SLAUGHTER: I think there would be a different point of view on your left. Dr. Uhlmann?

DR. UHLMANN: I shall try to limit this to a few remarks relating to our routine procedures. Let me state first that there is considerable difference between the end-results in carcinoma of the breast as reported from large medical centers by highly skilled surgical teams who have accumulated experience in performing such surgery, and the end-results in cases treated in a general hospital where many surgeons with varying skill carry out the operations. Statistically, 60 per cent of the cases referred to us for treatment of carcinoma of the breast are in an operable stage, and 40 per cent are inoperable. On the basis of studies of 312 patients followed for a period five to ten years, we believe that the most opportune

time for beginning radiation therapy for carcinoma of the breast is within six to ten days after radical mastectomy. This routine was followed in all the 312 patients who were operated on by 23 different surgeons, gynecologists, and general practitioners. If, as stated in the referral notes, all these patients had Halsted operations, then there must have been considerable variation in the Halsted procedure, because some of them had had only local excisions or, at best, a simple mastectomy. Fifty per cent of these patients were operated on by the most competent surgeons, and the procedures were comparable to the best surgery carried out in this country. However, when the end-results in the patients who underwent competent surgery and in those who had less competent surgery were analyzed, it was found that there was no material difference in survival rates. We believe that the group operated on less competently benefited by postoperative radiation, which compensated for the lack of surgical skill in keeping the local recurrence rate down to 14 per cent. The five-year survival rate with such management of operable patients was approximately 50 per cent. We are aware of the fact that postoperative radiation is a procedure effective only locally. In all patients who are still in the child-bearing age and who are menstruating regularly, we advocate irradiation of the ovaries for castration purposes. The exception is in patients who have microscopically a mucinous adenocarcinoma of the breast. It has been our experience that these tumors, like primary carcinomas of the stomach with identical histologic features, have a preference for metastasizing to the ovaries. Therefore, we recommend oophorectomy in such patients.

In addition to radiation therapy, we recommend the use of androgens for the treatment of the skeletal metastases of breast carcinoma, and of estrogens for the treatment of soft-tissue metastases. We also have used nitrogen mustard and P-32. Otherwise, we follow the principles mentioned previously.

MODERATOR SLAUGHTER: Dr. Taylor, we have covered in chronologic order the treatment of mammary cancer. Everyone seems to agree that endocrine substances should be withheld until all other methods of treatment are exhausted, and that then they will prove useful. Have you anything to add?

DR. TAYLOR: No, I have nothing to add.

DR. SCHMITZ: May a gynecologist ask a question about the gonads? I have a particular respect for them, and have never subscribed to the idea that at age 40, 50 or 60 years the gonads should be removed. If Dr. Uhlmann believes that the ovaries need not be removed, that is fine. I have been interested for a long time in the ovaries of patients who have been heavily irradiated and then hysterectomized without removal of the gonads. I believe that radiation therapy cannot substitute for castration in the case of interstitial destruction of the ovary. In prostatic carcinoma, for many years we irradiated the testes, the spine, and the bony girdle in the region of the testes. The patients were not appreciably benefited. Huggins removed the male gonads and obtained marked improvement. Is there some difference?

DR. TAYLOR: May I bring up a point? Smith and Smith in Boston have assayed urinary estrogens after supposedly adequate radiation therapy to the ovaries. They found a much higher excretion of estrogens in this group of patients than in those surgically castrated.

DR. UHLMANN: I do not believe that it is possible to make a comparison between cancer of the ovaries and cancer of the prostate. The therapeutic methods used for these two localizations of cancer are quite different, and seldom is the transurethral or perineal resection of carcinoma of the prostate followed by radiation therapy. It has been our experience that patients with carcinoma of the prostate are reluctant to have their testes surgically removed or treated by irradiation. The prevalent belief is that with the loss of the testes or their function the patient may become impotent. In rare instances, we have given radiation therapy to the testes following prostatectomy or after partial resection of the prostate. In some instances, this was followed by a gratifying temporary response.

MODERATOR SLAUGHTER: Don't you think, too, that there is considerable variation in the effect on the ovary according to the dosage used? Dr. Schmitz hinted at it when he referred to patients treated by irradiation for cancer of the uterus. Of course, that was high dosage. It is observed clinically that patients with breast cancer that has spread to the pelvis and to bone do far better after irradiation of these metastatic lesions than does the patient who is simply castrated, that is, with the usual dose of irradiation just large enough to cause the cessation of menses. From 900 to 1200 roentgens applied to the skin is not high dosage, but a 3000 or 4000 roentgen tumor-dose to the pelvis is quite a different matter.

DR. UHLMANN: Commenting on the question of whether irradiation of the ovaries for castration purposes is preferable to surgery, it is difficult to make any definite statements. Helpful in appraising this problem is a publication from the Memorial Hospital in New York, concerning over 100 patients treated with irradiation and a similarly large group treated by surgical castration. Comparison of results was based upon the influence of either method on proved skeletal metastases as visualized in roentgenographic films. The improvement following castration was between 12 to 14 per cent, regardless of method. It is our concept that, if there is no difference between results with the two procedures, we prefer radiation therapy.

MODERATOR SLAUGHTER: What about castration in postmenopausal patients?

DR. TAYLOR: We have performed oophorectomy on 16 postmenopausal women, and obtained regression of the tumor in only 1 patient whose postmenopausal period was of four years' duration. It is usually pointless to perform an oophorectomy on a patient 60 years of age.

MODERATOR SLAUGHTER: Lymphomas in themselves present a great problem in palliation.

Dr. Bricker, do you operate in the case of lymphoma? Has surgery a place in the management of lymphomas?

DR. BRICKER: I do operate on lymphomas arising in the abdominal viscera. Many of these lesions appear to be localized, and can be controlled by radical removal. Therefore, when encountered in the abdomen in an operable stage the treatment of choice is surgical removal. However, in the case of advanced lymphosarcoma of the stomach I would hesitate to recommend total gastrectomy, since the procedure could only be considered as a palliative one, and since better palliation might be achieved by other measures, namely irradiation therapy. Malignant lymphomas of the small intestine or colon that have metastasized

to the root of the mesentery are not amenable to surgical excision and are better treated by irradiation therapy, unless surgical relief of obstruction is necessary. It is important before performing a total gastrectomy for neoplasm to verify the diagnosis by microscopic examination since, if the lesion is found to be a malignant lymphoma and is of an advanced nature, one might be more inclined to rely on irradiation therapy than surgery.

MODERATOR SLAUGHTER: The surgical literature shows that the cure rate for lymphoma of the stomach is considerably higher than that for carcinoma of the stomach. I was thinking of the treatment of Hodgkin's and localized diseases. There is a trend throughout the country toward removal of localized lymphoma, particularly that of the Hodgkin's type. We have had about 18 cases with long-term survival, but these cases are rare. The patients must be well chosen if the procedure is to be of any use.

Dr. Uhlmann, what is your practice in treating lymphomas?

DR. UHLMANN: I agree that most patients with gastro-intestinal lymphosarcoma are candidates for surgical exploration and, if possible, resection. Primary lymphosarcomas of the gastro-intestinal tract have a pattern of biologic behavior which is different from that of other lymphosarcomas. This is mainly true for the small-cell lymphosarcoma and less so for the other lymphoblastomas that are often summarily classified as malignant lymphomas. Reports in the literature show that patients with Hodgkin's disease have survived ten, fifteen or twenty years after initial treatment. We also have observed such long survivals in patients with tumors of the lymphoblastoma group. In many instances, we could prove that these patients originally had giant follicular lymphadenopathy (Brill-Symmers disease) that had developed into lymphosarcoma or Hodgkin's disease. When a true malignant lymphoma originates as Brill-Symmers disease and receives proper and intensive treatment, apparently it can be controlled in a large number of patients. In our experience with this group of patients, a considerably higher percentage survive without symptoms for five, ten or fifteen years or more.

I should like to mention one other observation that has an important application. In many patients with leukemia, the basal metabolic rate is elevated, sometimes to +50 per cent and higher. We have noticed that the elevation of the basal metabolic rate often precedes the onset of clinical symptoms. When proper therapy is given, the basal metabolic rate is reduced to normal long before clinical symptoms disappear. In patients manifesting this relationship, we have found it advisable to be guided as to the amount and timing of therapy by carefully watching the basal metabolic rate. It has thus been possible to reduce the amount of radiation administered and to stop treatment at a time when clinical symptoms have not yet disappeared. We have noticed that the group of patients treated in this manner survived longer and became resistant to therapy at a much later date, if at all.

ACCIDENTS AND THE AGING

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With the relative and absolute increase in the older age segments of the population of the United States has come a heightened interest in degenerative health conditions, for it is these diseases which so frequently mar the so-called golden years of life. That a considerable amount of mortality and morbidity in this age group accrues from a non-degenerative health condition—accidents—has largely escaped notice by the health professions.

Although none would deny the importance of cardiovascular disease, cancer, arthritis and rheumatism, and the related chronic disorders to our aging citizens, considerable evidence can be mustered to indicate that safety for the aging merits the attention and study of the gerontologist and the geriatrician.

EXTENT OF ACCIDENT PROBLEM

Since 1948, total accident deaths in the United States have varied between 90,000 and 96,000 per year. On the average the number has been about 93,000 deaths per year and the rate per 100,000 population has been approximately 56 to 58. The number of accident deaths experienced by those past 64 years of age has remained fairly constant at 25,000 to 26,000 each year. This means that 1 out of each 4 accidental deaths involved a person classed as a member of the aging population group. If one considers the next younger age group—55 to 64 years of age—one finds an additional 8,000 deaths on the average; and if the accident experience of those 45 to 54 years be added, then over 40,000 deaths each year are attributable to accidents in persons 45 years of age and older. These deaths accounted for some 49 per cent of all accident deaths in the United States (1).

Because there is no system for nationwide collection of information about all accidental injuries, there is a dearth of information about the non-fatal accident experience of the entire population. However, morbidity studies conducted in localized areas of this country indicate an equally significant number of accidental injuries by those in the middle and late periods of adult life (2).

That these considerable rates of mortality and morbidity have escaped general notice may be attributed to at least three factors: First, although the number of accidental deaths in all age groups has remained fairly constant, the population has undergone a sustained increase, so that rates of accidental death in the various segments of the population have shown some decline; a declining rate may be construed as indicative of success in control efforts and may have dampened interest in initiating further study and activity.

Secondly, although persons in the middle and late periods of adult life ex-

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perience the greatest number of accidental deaths of any age group, mortality from other causes increases in this period to the extent that, relatively speaking, accidents become of less importance. All recognize cardiovascular-renal diseases as the major cause of deaths, and the ranking of accidents as the fourth or fifth leading cause of death may lead to the erroneous conclusion that efforts here can be deferred until later.

In the third place, greatest attention of safety specialists in many areas has been centered about the significance of accidents to the younger population. In the years of life from 1 through 34, all the forces of mortality are less significant than in later years, so that even a moderate number of accidental deaths carries heavy relative weight in determining major causes of death. For example, in 1954, the age groups from 1 through 34 years experienced approximately 30,000 accidental deaths, and for all these age groups accidents ranked as the leading cause of death. In that same year, among persons past 45, accidents ranked as the fourth leading cause of death; yet among these age groups there were approximately 44,000 accidental deaths.

Transportation versus non-transport accidents

Major emphasis in the United States presently is centered around transportation accidents, particularly those involving the motor vehicle. Transportation accidents account for slightly less than half of all accidental deaths in an average year in this country, with the motor vehicle involved in from 90 to 95 per cent of transportation accidents. For example, in 1954 transportation accidents claimed 41,615 of the total of 90,032 accidental deaths that year. Of the 41,615 transportation deaths, the motor vehicle was involved in 38,301, water transport accidents in 1,498, aircraft accidents in 1,450, and road vehicles other than the motor vehicle in 366 deaths (3).

Emphasis on motor vehicle accidents is another factor which has turned attention away from the true accident problem of the older citizen, since the transportation accident problem is considerably less serious for him than are accidents occurring in other settings. In 1954, for the general population, transport accidents accounted for 46 per cent of all accidental deaths, but for persons past 45 years only 36 per cent, and for those past 65 only 25 per cent.

Table 1 shows accidents in persons past 45 years of age for the year 1954. It reveals that almost half of the 90,000 accidental deaths that year were among those 45 years of age and over. This age group comprises about 30 per cent of the total population of the United States; thus, it may be said that 30 per cent of the population undergo 50 per cent of all accidental deaths, and this high-incidence group is made up of those past 45.

Table 1 shows the declining importance of transportation accidents as age increases. Conversely, one should note the increasing importance of non-transport accidents as age increases. Particular emphasis should be laid on the facts that in 1954: 1) home, farm, and resident institution accidents caused some 58 per cent of the non-transport accidental deaths, and 2) 2,700 deaths occurred from accidents in resident institutions such as asylums, hospitals, nursing homes, boarding homes and rest homes.

TABLE 1

Accidental Deaths, All Ages and Age Groups 45 Years and Older, by Transport, Non-Transport, Home-Farm and Resident Institutions, United States, 1954

Age	Total All Accident Deaths	Number Transport Accident Deaths	Per cent of Total Deaths Due to Transport Accidents	Number of Non-Transport Accident Deaths	Per cent Total Deaths Due to Non-Transport Accidents	No. of Non-Transport Accidents Occurring in Homes and Farms	No. of Non-Transport Accidents in Resident Institutions	Per cent Non-Transport Occurring in Homes and Farms and Resident Institutions
All ages	90,032	41,615	46	48,417	54	25,211	2,735	58
45–54	9,326	4,882	52	4,444	48	1,914	100	45
55–64	8,973	4,414	44	4,559	56	2,173	195	52
65–74	9,652	3,742	39	5,910	61	3,389	493	66
75–84	10,130	2,179	21	7,951	79	4,803	1,008	73
85 & over	5,686	456	8	5,230	92	3,284	711	76
Total over 44 years	43,767	15,673	36	28,094	64	15,563	2,507	64

From: "Accident Fatalities, U. S. and each State, 1954." Vital Statistics-Special Reports, Vol. 44, No. 16, Oct. 5, 1956, National Office of Vital Statistics, Public Health Service.

It is these latter two sites of accidental death which are of most importance to the older persons in the population. Retirement practices, employment policies, and a lack of recreational opportunities all have resulted in the senior citizens spending more and more time at home. Coupled with this is perhaps some lessening in interest in the world at large plus major or minor long-term illnesses which have placed even greater restrictions on the older person being at large in the community. Recent years have seen interest mount in home-care programs, particularly for the elderly, and the increased accident hazard of the home has, to some, made this a mixed blessing. That the team of specialists providing home-care services should include a home-safety expert is a recommendation not completely unworthy of consideration.

The mounting population in resident institutions has been one of the hallmarks of the aging population, and the 2,500 deaths in such institutions among persons past 45 constitute over 90 per cent of all accidental deaths in these locations. With a few notable exceptions, those with responsibility for the licensing, inspection and supervision of these institutions have failed to put appropriate emphasis on this phase of the institutional environment.

Table 2 shows the most common types of non-transport accidents recorded in the United States, in terms of the totals for all ages and for those past 45 years. A high percentage of the deaths from falls, fires, poisonings, and firearms occur either in the home or in resident institutions. A significant number of other non-transport accidents occur in the home, with the exception of drowning, of which only a small percentage occurs in homes. The proportion of these non-transport accidents involving persons past 45 varies from 89 per cent in the case of falls, to 21 per cent in the case of drownings, with the overall average of 58

TABLE 2

Non-Transport Accidental Deaths, All Ages and Over 45 Years, Percentage Among Those Over 45, by Type of Accident, United States, 1954

Accident Type	All Ages	Total 45 and Over	Per Cent 45 and Over	45–54	55–64	65–74	75–84	85 & Over
All non-transport accidents	48,417	28,094	58	4,444	4,559	5,910	7,951	5,230
Falls	19,771	17,545	89	1,178	1,801	3,598	6,305	4,663
Fire and explosion	6,083	2,896	48	690	603	774	628	201
Poisons—solids and liquids	1,339	474	35	228	132	83	24	7
Poisons—gas and vapor	1,223	675	55	224	171	169	93	18
Firearms	2,281	595	26	276	197	84	35	3
Blow from falling object	1,255	517	42	237	167	75	30	8
Machinery	2,009	886	44	357	343	140	42	4
Electric current	965	213	22	125	60	24	3	1
Drowning	5,049	1,079	21	396	348	218	100	17
Other		3,214		733	737	745	691	308

From "Accident Fatalities, U. S. and Each State, 1954." Vital Statistics-Special Reports, Vol. 44, No. 16, Oct. 5, 1956, National Office of Vital Statistics, Public Health Service.

TABLE 3

Non-Transport Accident Death Rates, United States, 1954, for All Ages and Selected Age Groups 45 Years of Age and Older, by Major Type of Accident—Rate per 100,000 Population

Accident Type	Rate: All Ages	Rate: 45–54	55–64	65–74	75–84	85 and Over
Poisons—solids and liquids	0.8	1.2	0.9	0.9	0.6	0.9
Poisons—gas and vapors	0.8	1.2	1.2	1.8	2.5	2.4
Falls	12.3	6.4	12.6	38.9	169.3	615.2
Blow from falling object	0.8	1.3	1.2	0.8	0.8	1.1
Machinery	1.2	1.9	2.4	1.5	1.1	0.5
Fire and explosion	3.8	3.7	4.2	8.4	16.9	26.5
Hot substances, steam, etc.	0.5	0.4	0.5	0.9	2.6	5.7

From "Accident Fatalities, U. S. and Each State, 1954." Vital Statistics-Special Reports, Vol. 44, No. 16, Oct. 5, 1956, National Office of Vital Statistics, Public Health Service.

per cent of all non-transport accidental deaths among those in the middle and late adult periods of life. The number of accidental deaths in most instances decreases with increasing age, since one finds fewer and fewer persons alive in the older age groups, However, in many instances the death rate (based on the number of those who are living in each age group) actually goes up. For example, the death rate from falls in persons past 85 years of age is over fifty times that of the population at large. Substantial increases have been recorded in connection with accidental poisonings with gases and vapors, death from fires and explosions, and in miscellaneous accidents (Table 3).

POSSIBLE CAUSES OF HOME ACCIDENTS

Leading opinion among health and safety specialists at the present time centers about the etiology of accidents involving two types of causative factors. These factors may be called the "personal" and the "environmental." The former is a term which describes those physical, emotional, mental and social attributes of the individual which serve to lower his accident threshold. The latter refers to hazardous or semi-hazardous conditions within the environment—be the environment that of occupation, transportation, or the home. It seems most logical to picture accidents as the result of a combination of personal and environmental factors, since placing an accident-liable individual in an environment seeded with hazards seems particularly conducive to the production of an accident with resulting injury or death. It is difficult to weigh the relative importance of these two etiologic factors in each accident. Depending upon current thought, safety activities have alternated between safety education and environmental control of accidents. Only when the importance of both are recognized may one anticipate effective accident prevention. The entry of physicians and other health specialists into the safety field holds promise of insuring that greater emphasis will be placed on the personal factors than has been the case in many safety activities in the past.

In considering the personal etiologic factors which may be of significance to the aging population, at least two seem of particular importance: 1) physical conditions which may lower the accident threshold, and 2) the older person's failure to recognize his inability to carry on activities at the same rate and intensity as he formerly did (4).

In the study of physical conditions which may increase the accident susceptibility of the individual, much attention has been directed to the slight, but measurable impairment of physiologic functions which may begin as early as the twenties and reach fairly significant levels after the age of 60. Physiologists state that in many persons these changes may be manifested by physical weakness, loss of coordination, or easy fatigability.

Another physical factor is the disability which may accompany any acute or chronic illness. Few older persons are blessed with an unlimited span of sickness-free years, and relatively minor illnesses, such as those of the upper respiratory tract, may stubbornly resist therapy. Certain studies of accidents among the aged have suggested that such physical conditions as cardiovascular diseases or disorders of the musculoskeletal system, may play a major role in many accident fatalities (5).

Another physical factor to be considered is the impairment of sensory functions, especially the loss of visual acuity. Failure to have visual defects corrected, wearing of improperly prescribed or fitted glasses, or perhaps difficulties inherent in adjusting to bifocal or trifocal lenses can, and do, contribute to accidents of all types in all age groups. Because the incidence of visual difficulties tends to increase as one grows older, it is a significant factor in considering the accident experience of older persons. Diminution of the senses of hearing and smell also predisposes to failure to hear or smell warnings of impending danger.

The second major factor—failure to recognize the inability to carry on former

activities—is more complex, and it may be a manifestation of a person's entire mental and emotional acceptance of the aging process. This may relate to the older person's inability to focus attention as forcefully as formerly, or it may be concerned with his failure to remember the need to be cautious in undertaking many tasks. At other times, this condition is demonstrated by a proud refusal to accept assistance in meeting everyday needs.

PREVENTION OF HOME ACCIDENTS

The fundamentals of preventing home accidents among the aged are the same as for those in any other age group. They involve first, a modification in an individual's behavior pattern, and second, an alteration in the environment in which he works and lives. The objective is to help people to develop positive safety habits and attitudes, and to create an environment which is as nearly free of hazards as possible.

In attempting to establish an environment which is favorable to the accident-free growth and development of children, we have recognized the importance of working primarily with the parents. Health and safety workers have not yet accepted completely the importance of directing their approach to those adults who are responsible for the older persons in the household, although Chapman has advocated that all family safety activities be channeled through the "index" person in each household (6).

The situation regarding older persons is different in one important aspect. In order to make a successful approach to the younger adults in the household, a step-by-step educational program must be directed to the older person at the same time. Occupational safety specialists have long recognized that the availability of the finest safety equipment will not reduce the incidence of accidents unless workers are taught the reasons why such equipment is needed and the advantages of using it. The same augmenting effort is mandatory for successful accident prevention in homes where aged persons reside.

In approaching the older resident in a home or institution, the health specialist must help him to develop certain specific attitudes toward accident prevention. This entails much more than a general admonition to "be careful about accidents," which may induce no reaction, or only anxiety. Included among the habits and attitude patterns which are important for the older person to develop are:

1. Regular work and social schedules which do not conflict with the need for rest and sleep.

2. Recognition of periodic variations in energy, and the ability to adjust work and recreation to these variations.

3. Recognition and acceptance of limitations in the amount of work which can be accomplished, and the need to reduce the speed with which work can be completed.

4. Realization that there may be a diminution of visual and auditory senses associated with the aging process, and an understanding of why these defects should be corrected.

To "safety condition" the environment for the older person, members of the household who are responsible for his well-being may use these guides:

1. Provide him with a living area in the home where the need to climb stairs is reduced to a minimum.
2. Install handrails on all stairs, both inside and outside the home, especially in the cellar.
3. Keep stairs clear of objects and obstructions.
4. Install easily accessible light switches at both the top and the bottom of stairs, and provide lighting which will sufficiently illuminate the top and bottom steps.
5. Provide beds of sitting height and secure them so that they do not move or roll.
6. Remove such obstacles as footstools, electric cords, and other low furniture from the rooms which the older person uses. Sufficient light should reach all areas in these rooms, and particularly, a light should be placed near the bed and over the medicine chest.
7. Fasten rugs and carpets throughout the house securely. Slippery wax should not be used on the floors.
8. Keep clothing, such as dress hems and pants cuffs, mended. Shoe heels should be of rubber and be replaced as needed.

When teaching the older person how he can help himself to live out his life safely, one should include in the program such common-sense but important precautions as these:

1. Walk carefully, especially up and down stairs.
2. Refrain from lifting or moving heavy objects.
3. Avoid taking hot baths and be careful about getting in and out of the bathtub.
4. Avoid standing or moving when feeling faint or dizzy.
5. Ask for assistance when lighting or refueling stoves, furnaces, heaters, and fireplaces.

With each contact between the private physician and patient, the health department and the family, and the social agency and the client, there exists an educational potential which presents an opportunity for effective safety education. Many now question the value of so-called safety programs which are built upon mass media of communication and there is a growing sentiment that success in accident control will come through the use of more traditional educational methods. Paramount among these is face-to-face teaching, either in the classroom, the physician's office or the patient's home. In this approach to safety education it is possible to envision a unique contribution which physicians, nurses, and a wide range of health-agency employees may make to the safety movement in America.

It is to be hoped that in making this fresh approach to accident control, appropriate efforts may be extended to those in the middle and late adult periods of life, since accidents are yet another force which stands to rob these individuals of many of the blessings of an increased span of life.

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THE VALUE OF ENDOCERVICAL CURETTAGE IN EARLY DIAGNOSIS OF CERVICAL CARCINOMA

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At the present time the treatment of the later stages of carcinoma of the cervix yields poor results, even when it is carried out by the most skilled individuals under the most ideal circumstances. Treatment of the early stages of the disease, however, produces results which are much more satisfactory. For this reason, early diagnosis is of the utmost importance. In cases of early carcinoma of the cervix the physician should be able to make the diagnosis by techniques readily available.

Many early cases will be missed if the physician uses these techniques only on patients who have some suspicious symptom or in whom the cervix appears abnormal. As many early cervical carcinomas are asymptomatic and are not detectable by visualization of the cervix (either because of the minimal changes produced, or the fact that these changes are hidden within the cervical canal), it is mandatory that patients be screened by these techniques in order to obtain the proper percentage of early diagnosis. The physician who does not carry out any of these procedures on patients who are asymptomatic or who have an apparently normal cervix will achieve an early diagnosis rate which is considerably smaller than it need be.

VAGINAL AND CERVICAL SMEARS

The Papanicolaou smear technique is extremely useful in screening patients for cervical carcinoma. There are many methods of obtaining material for such smears. According to the method of Papanicolaou and Traut (1), we use glass pipets to obtain a vaginal and a cervical smear on each new patient, and at intervals of six to twelve months on each old patient. Of the two smears, the cervical one is the more important. The patients should not take a douche for at least twenty-four hours before the smears are taken. In the vagina, the most readily available material for aspiration smear is in the "pool" in the posterior fornix. The cervical aspiration material is obtained primarily from the cervical canal.

When an obvious carcinoma is present, Papanicolaou smears are not necessary for diagnosis. In such cases there is no doubt as to the area from which biopsy specimens should be taken. The greatest diagnostic use of Papanicolaou smears is in the case in which there is no obvious lesion. Under these circumstances, a small lesion can be easily missed by biopsy, but the Papanicolaou smear obtains a sample of cells representing the entire desquamating area of the cervix. False negative results are rare; Graham and associates (2) state that they are relatively evenly distributed among the various stages of the disease, whereas false negative

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biopsy findings are more frequent in the early stages. Smears reported as "unsatisfactory" should be repeated.

False positive results are reported occasionally, and should be verified by tissue studies before a final diagnosis is made. Another reason for such verification is that smears do not furnish information as to the location of the tumor on the cervix, nor can invasiveness be determined by this technique.

The Class 3 ("suspicious") smear is an important category. The patient should be followed closely by repeated smears and tissue studies in order to rule out the diagnosis of carcinoma (Class 4 or 5 smears).

In 1956 Clarke and Gilmore (3) reported a series of 219 cases of carcinoma of the cervix from the Syracuse Memorial Hospital. Among the cases in which smears were taken, 96.7 per cent had smears in Classes 3, 4, or 5. In clinical Stage 0 of the disease, 66.7 per cent of the patients had positive findings, and 27.8 per cent had "suspicious" findings. In clinical Stage I of the disease, 94.1 per cent had positive, and 2.4 per cent had "suspicious" findings in the smears.

CERVICAL BIOPSY

The Schiller test is useful in determining the sites of cervical biopsy. If carcinoma is present in a Schiller-treated area it will always stain Schiller-light, but even so, a very small carcinoma may be easily overlooked. The Schiller stain is of little aid in locating carcinoma hidden in the cervical canal. In such cases colposcopy and colpomicroscopy are also of limited value.

The recommended method of performing portio biopsies in searching for cervical carcinoma is to take a specimen from each of the quadrants of the cervix at the squamocolumnar junction. If in doubt, the squamocolumnar junction may be highlighted by means of the Schiller stain. Additional biopsy specimens should also be taken from Schiller-light or otherwise clinically suspicious areas.

In a series in which biopsy specimens were obtained routinely in this manner (3), the results were positive in 86.9 per cent of patients with cervical carcinoma. In clinical Stage 0, the results were positive in only 65 per cent and in Stage I, 84 per cent. The main reason why so many early cases of cervical carcinoma are not diagnosed on the basis of punch-biopsy findings is that the carcinomatous portion of the cervix is frequently missed by the biopsy punch.

ENDOCERVICAL CURETTAGE

The use of endocervical curettage as a technique in diagnosis of carcinoma of the cervix is based on the belief that many cervical carcinomas originate on the canal side of the squamocolumnar junction. Gusberg (4, 5) found the portio vaginalis involved in only 14 of 51 cases of Stage 0 carcinoma. In mapping out 73 cases of cervical carcinoma he found none involving the portio vaginalis alone. In the cases in which the initial site of invasion could be determined, the origin was apparently on the canal side of the squamocolumnar junction. Once invasion had occurred, the tumor seemed to spread by concentric expansion, frequently reaching the parametrium before it appeared in the portio vaginalis; its spread to the latter area appeared to be a matter of chance and contiguity. No tumors

were seen arising in the portio and spreading upward. Pund (6) stated in 1946 that cases of carcinoma *in situ* studied by him were found mainly or entirely in the gland-bearing portion of the cervical lining. For these reasons, endocervical tissue should practically always be studied in conjunction with cervical biopsy specimens in attempting to diagnose cervical carcinoma.

Several methods of obtaining endocervical tissue for examination have been proposed. The important thing is that an attempt be made to obtain such tissue. The technique we have used consists in scraping the endocervical canal from the external os to the internal os with a small curette having a head about 5 mm. in diameter, in much the same manner as the endometrium is scraped during a dilatation and curettage. Before this is carried out, the patient should be warned she will experience a few cramps. Every effort should be made to get all of the material obtained, including blood clot, into the bottle of fixative. There are several methods of collection. One is to deposit the material on the thumb of the gloved hand which holds the speculum, by tapping the curette on it after every few scrapes; when the curettage is completed the material can be scraped off the thumb into the bottle of fixative. Another method is to collect the material in the depression in the posterior blade of the speculum and then transfer it to the bottle of fixative after the curettage is finished.

To attain good results with endocervical curettage, it is essential that the pathologist get every speck of the curetted material into the wax block from which slides are cut. This may be done by first straining the contents of the specimen bottle through a fine mesh cloth and then folding this cloth over the material remaining on it. After further fixation, every bit of tissue on the cloth should be embedded in the wax block. When the curettage is performed in the operating room, the material may arrive at the laboratory in a piece of gauze. From this specimen, every speck of material which can be seen should be picked and placed in fixative; then the gauze may be immersed in the fixative and shaken in order to loosen any tiny bits of tissue which may remain on it.

After the first slides are made, the block should be saved in case additional cuts are necessary because 1) atypical tissue is seen which raises the possibility of carcinoma, or 2) carcinoma is noted, but the presence or absence of invasion cannot be determined. If recuts do not solve the problem, all the diagnostic tests should be repeated. Before repeating the endocervical curettage, though, it is best to wait from six weeks to three months in order to give the denuded endocervix a chance to recover. Results will not be as good if recuretting is carried out sooner than this.

If repeated examinations of smears, biopsy specimens, and endocervical curettings still leave the diagnosis undecided, the tests should be repeated under anesthesia, so that more vigorous endocervical curettage and dilatation and curettage of the uterine cavity may be performed. In such cases the endocervical curettings should always be obtained before the cervix is dilated in order to avoid traumatizing the endocervical tissue. The endocervical and endometrial tissues should be kept separated. Multiple sections should be made of all tissue obtained.

No case diagnosed as carcinoma *in situ* by means of cervical punch-biopsy

should be treated without examination of endocervical tissue, because of the possibility of invasive carcinoma in the cervical canal.

In cases of cervical stenosis, endocervical curettage may be difficult. These cases should not be neglected, however, as the stenosis may mask or even be caused by a carcinoma. It is necessary to anesthetize the patient in order to obtain endocervical curettings in some cases of cervical stenosis.

The one contraindication to endocervical curettage is pelvic inflammatory disease of any activity, as the inflammation may be aggravated by the endocervical manipulation. Even in cases in which pelvic inflammatory disease is only suspected, we do not perform endocervical curettage if the erythrocyte sedimentation rate is elevated.

The procedure may be carried out during pregnancy if the necessity is indicated by Papanicolaou smears. Great care should be taken in such cases to avoid passing the internal os.

As reported in a previous paper (3), endocervical curettings yielded positive findings in 94.6 per cent of a series of patients with cervical carcinoma. In Stage 0, the findings were positive in 89.5 per cent, and in Stage I they were positive in 94.6 per cent. These results are better than those obtained with punch biopsies. When both cervical biopsies and endocervical curettings are obtained, a correct diagnosis should be made in 98.7 per cent of cases. When one of these procedures is carried out, there is practically no added effort in carrying out the other. The comparative value of the two procedures is demonstrated again by the observation that in each of the first three stages of the disease the percentages of positive curettage and negative biopsy findings are greater than the percentages of positive biopsy and negative curettage findings. The discrepancy between the percentages in these two categories becomes progressively greater with each earlier stage. In Stage 0 of the disease, 31.5 per cent of cases have positive curettage and negative biopsy findings, whereas the opposite is true in only 5.3 per cent. These figures do not imply that the one technique should be used to the exclusion of the other. Both should be performed.

CERVICAL CONIZATION

Conization of the cervix is the final diagnostic aid to be mentioned. This technique has been advocated 1) as an aid in diagnosis when the suspicion of carcinoma has been raised by one or more of the aforementioned techniques but the diagnosis is still not confirmed, 2) as an aid in determining the presence or absence of invasion when doubt remains following other techniques, and 3) as a follow-up procedure when the diagnosis of carcinoma *in situ* has been made by other methods.

In taking the cone of tissue from the cervix, the apex of the cone should extend all the way up to the internal os. This may be difficult. In any slide made from a cone of tissue taken from the cervix, the epithelial-stromal relationships of the tissue may be preserved better than they are in a slide made from endocervical curettings. This is the main advantage of conization over curettage. In slides made from curettings, the tissue relationships are frequently disrupted, but they are usually sufficiently preserved in enough areas to permit a diagnosis of carci-

noma and to determine the presence or absence of invasion. The advantages of curettage over conization are: 1) curettage is usually an office procedure, is simpler and less traumatic than conization, and does not tend to cause cervical stenosis or other difficulties; and 2) on any one slide of material obtained by cervical curettage there is a more general representation of the entire endocervix than on any one slide of tissue obtained from a conized specimen. The second factor may facilitate diagnosis from a laboratory viewpoint, in that many less slides may be required. However, when the diagnosis is still in doubt after repeated attempts using other techniques, conization of the cervix may be a wise procedure.

SUMMARY

Early diagnosis of carcinoma of the cervix is the greatest contribution the clinician can make at present toward determining a favorable prognosis in this disease. To obtain the greatest possible percentage of correct diagnoses while the disease is still in the early stages, it is necessary to perform screening tests rather than wait for the development of symptoms or signs.

The Papanicolaou cytologic smear technique is a valuable screening procedure, as the results will be positive, or suspiciously so, in 96.7 per cent of patients with cervical carcinoma. However, studies of cervical tissue are required for confirmation of the diagnosis and determination of the presence or absence of invasion. Routine quadrant biopsies of the cervix will yield positive findings in 86.9 per cent of patients with cervical carcinoma. Endocervical curettage has an advantage based on the fact that many cervical carcinomas originate on the canal side of the squamocolumnar junction where they may be inaccessible to the biopsy punch, Schiller stain, colposcopy or colpomicroscopy. This procedure, which is simple and may be performed in the office, yields positive results in 94.6 per cent of patients with carcinoma of the cervix. The advantage of endocervical curettage over cervical biopsy is especially prominent in early cases. A combination of the two techniques furnishes diagnostic findings in 98.7 per cent of cases. If the diagnosis is still in doubt after the foregoing tests have been repeatedly performed, conization of the cervix may be of value.

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HOST-TUMOR ANTAGONISM. VII. MULTIPLE PRIMARY MALIGNANT NEOPLASMS. DOES THE INITIAL GROWTH IMMUNIZE AGAINST, OR PREDISPOSE TOWARD A SECOND LESION?*

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I. STATEMENT OF THE PROBLEM

It would be of great interest to know if the chance of a second primary cancer developing in a cancer patient is greater, the same, or less than the chance of a primary cancer developing in a normal person. If there is more chance of a second primary lesion developing in a cancer patient, then there is increased susceptibility; if there is less chance, then it might be assumed that the original cancer confers some degree of immunity. Some authors believe that the incidence of multiple cancers does not differ from the general incidence of cancer in a normal population.

Peller (1), using statistical methods, found that among patients with certain occupational cancers, there was a decreased incidence of cancers of other organs. He, therefore, believed that cancer in one organ results in the development of immunity in other organs. In a later study (2), using material from the U. S Navy, he found an increased incidence of lip and skin cancer because of increased exposure to the sun's rays, and a greatly diminished incidence of cancer in other organs.

In a recent book entitled "Cancer in Man," Peller (3) states his immediate solution to the entire cancer problem. He contends that a cancer control program can be based on deliberate efforts to encourage the development of skin cancer by actual exposure. Since skin cancer is curable in most cases, this procedure would presumably result in immunity to the development of the highly fatal cancers of the internal organs. He alleges that this program would reduce cancer mortality by approximately 90 per cent.

Such a challenge should be thoroughly investigated. This essay is a review of the literature on this intriguing subject.

II. ANALYSIS OF THE DATA

Bugher (4) computed the expected occurrence of coincidental multiple primary malignant neoplasms from the cancer mortality data in the United States for the years 1920 through 1928. Comparison with the reported incidence of such cases showed that the actual incidence did exceed that expected from chance alone. According to Bugher's calculations, the expected rate of cancer deaths involving "double primaries" was 1.63 per cent for males and 1.58 per cent for females. These figures are based on chance alone; in many of the reports

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TABLE 1

*Incidence of Multiple Primary Malignant Lesions**

Author and Reference No.	No. of Cancer Cases Studied	No. with Multiple Lesions	Per Cent	Remarks
Ophuls (20)	512	15	2.9	Autopsy
Hanlon (5)	950	18	1.9	Autopsy
Warren & Gates (9)	1,078	40	3.7	Autopsy
Bugher (4)	983	30	3.1	Autopsy
Burke (21)	583	46	7.8	Autopsy
Austin (22)	887	24	2.7	Autopsy
Kirshbaum & Shively (23)	1,411	25	1.77	Autopsy
Tullis (7)	1,044	21	2.0	Autopsy
Hurt & Broders (24)	2,124	71	3.3	Surgery
Stalker *et al.* (25)	2,500	113	4.52	Surgery
Owen (26)	3,000	143	4.7	Clinical
Ward (27)	1,773	94	5.3	Clinical
Schreiner & Wehr (18)	11,212	307	2.7	Clinical

* Modified from Tullis (7).

on autopsy series they are much higher. Bugher found 30 cases of multiple primaries in 983 cases of cancer, an incidence of 3.1 per cent. He believed that the apparent contradiction between theory and experience was understandable if the risk of acquiring cancer was not spread uniformly over the entire population, but over some large portion of it. Cancer morbidity and mortality rates based on this reduced population would indicate a frequency of coincidental cancer multiplicity in agreement with the actual occurrence. According to Bugher, this is equivalent to saying that there is an inherent susceptibility to cancer, not possessed by all people but still possessed by a large group. A partial review of the incidence of multiple primary malignant lesions is presented in Table 1.

Hanlon (5) believed that multiple primary carcinomas rarely occur in the same patient. He reviewed a series consisting of 18 cases found in 3,000 postmortem examinations (950 malignant tumors) at the Mayo Clinic and 31 cases in which a clinical diagnosis was made at the clinic. Hanlon concluded that multiple primary carcinomas represent incidental occurrences rather than a definite response to a law of neoplasm formation.

According to Welch (6), the incidence of multiple primary tumors is greater than could be expected by chance alone. He felt that if this fact be recognized, it would afford the patient the possibility of second surgical cure by avoiding the erroneous diagnosis of metastases. Knowing that the occurrence of multiple primary neoplasms is a strong possibility, he advocated that when cancer patients return for a check-up, they should have more than a routine examination for recurrence; there should be a thorough search for a possible second malignant tumor.

In the diagnosis of multiple primary malignancies, the microscopic sections should meet the following criteria (7):

1. Each lesion should possess the characteristics of malignancy.

2. Each lesion should have the histologic pattern commonly associated with a malignant growth in the tissue from which it comes.

3. Each lesion should be a distinct entity, and the possibility of it being metastatic should be ruled out as far as possible.

The literature usually excludes those tumors that have a known tendency to multicentric origin, such as multiple-cell carcinoma of the liver, simultaneous bilateral hypernephromas of identical histologic pattern, and simultaneous bilateral carcinomas of the ovary or breast which have the same histologic patterns. Bilateral lesions of the female breast that follow each other after an interval of time and are of different histologic patterns are usually included, however. Leukemias and Hodgkin's disease have usually not been included in reports because there has been no universal acceptance of these lesions as carcinomatous.

Undoubtedly there are more patients with multiple primary neoplasms than are reported in the literature, and the number in whom the condition remains undiagnosed and unreported must be large (8). A great many of these patients are never seen by a physician, particularly where diagnostic facilities are poor. Many others die of intercurrent diseases, before the second primary neoplasm causes clinical symptoms. Many other cases are not diagnosed because all tissues are not serially sectioned, and therefore the second primary tumor is missed at autopsy.

Another limitation to the accuracy of statistics in this disease, is the absence of definitive criteria that will always differentiate true multiple primary lesions from direct extension and metastases. Two tumors in paired organs may have the same histologic structure and still be multiple primary lesions. At present, such a situation would be considered as a metastasis. All of these factors tend to yield a lower incidence than actually exists.

Warren and Gates (9) analyzed the statistics of multiple primary malignant neoplasms, and concluded that the frequency of multiple malignancy was 1.87 per cent in all cases of cancer, based on all statistics. Based on American statistics, the frequency was 3.9 per cent, and in the authors' own series of 1,078 cancers, the frequency was 3.7 per cent. Their conclusion was that multiple malignant neoplasms occur more frequently than can be explained on the basis of chance alone. They believed that in a person with one cancer there is a greater chance for development of a second cancer than would be expected from chance alone. This implies a definite predisposition or susceptibility to cancer, or exposure to some influence favoring the development of cancer. The nature of this predisposition is not known.

Warren and Gates (10) in a later autopsy series comprising 2,829 patients, found 194 instances of multiple primary malignant growths—an incidence of 6.8 per cent. They concluded that a patient with one cancer is eleven times more prone to the development of a second primary cancer than is any other person to the development of an initial cancer. These authors found an average interval of 3.2 years between the first and second primary neoplasms.

Lombard, Levin and Warren (11) studied patients with multiple primary

malignant growths as determined from death records, morbidity records and records of patients who attended cancer clinics. They found that in approximately half of the patients with multiple cancers, other than cutaneous, the presence of the second primary growth was not known until after death. Therefore, the omission from statistics of the data on living patients furnishes a more accurate picture of the frequency of multiple primary malignant tumors.

Using the records of both the living and the dead patients in certain combinations, these authors found that the observed cases of multiple malignant growths exceeded the expected number. The "skin-skin" combination showed a strong predisposition to multiple malignant growths. Males with lip cancers appeared to have a predisposition toward the development of multiple cancers. It seemed fairly definite from their data that the presence of a skin cancer does not immunize the patient against the formation of a second primary cancer. They also listed a series of patients with multiple primary cancers and considered the relative frequency to be 4.5 per cent. This figure is more than twice the expected rate based on chance alone, as calculated by Bugher.

To most authorities, the finding of multiple malignant growths in a patient, means that that patient is more than ordinarily susceptible to cancer. At this point we should distinguish synchronous (simultaneous) from metachronous (consecutive) occurrence. Theoretically, these should be easy to distinguish, but practically the differentiation is very difficult. Peller (3) in his book states that Warren may have been dealing with synchronous tumors, but that one was diagnosed later than the other. This is indeed a problem, and is almost impossible of solution at the present time.

The study of Mider and his coworkers (11b) led them to the conclusion that in a patient successfully treated for a specific type of cancer there is at least as great a probability as in a non-cancerous subject of similar age and sex that another cancer will develop. Moreover, a second cancer of the same histogenesis may be expected to occur much more often than one would expect, on the basis of chance alone. However, they felt that their data did not bear out the contention that in the patient who survives one cancer there is a greater than average probability that another cancer will develop in a different organ of the body. It was suggested that the custom of fitting all the patient's symptoms into one disease entity be revised, especially if the patient has had cancer. These authors observed that in a significant proportion of the cancerous population, other diseases and other cancers develop which are not related to the initial cancer.

Barrett and his coworkers (8) noted a very intriguing point in their review of a series of multiple primary cancers. It appeared that the average time interval between the initial and subsequent primary lesions, confined to the large bowel, was seven years and four months. However, when the second primary lesion involved the ovary, the time interval was only seven months. In their experience, the latter had the poorest prognosis of any combination; thus it would seem expedient to castrate all female patients with carcinoma of the gastro-intestinal tract at the time of initial resection. Similarly, these authors noted that about 30 per cent of their cases of multiple primary growths involved the breast and

the reproductive organs. The ovaries were involved in 3 patients, and the uterine cervix in 8. Therefore, if it is the intention of the surgeon to castrate a patient with cancer of the breast, it would be better to remove the ovaries surgically. The other reproductive organs should be watched following treatment for carcinoma of the breast.

Hellendall (12) found 30 cases of multiple malignant tumors in 685 cancer autopsies (4.3 per cent). If these were synchronous cancers, they might indicate cancer susceptibility as Peller contends. Peller felt that he could differentiate synchronous from metachronous tumors to a great extent. It has been shown by many writers, including Phillips (13), that skin cancers are very often multiple. Peller (14) thought that these should be considered multicentric—*i.e.*, the occurrence in more than one area of a single primary cancer. Warren and Ehrenreich (15) calculated that the expected number of multiple malignant tumors in their series should be 17. Actually, they observed eleven times that number (194 cases), if chance alone were the factor. They felt that these data confirmed the existence in some people of an increased susceptibility to cancer.

Peller (2) stated, on the basis of the occupational mortality statistics of England and Wales, that an increase of carcinogenic irritation leads to an increase of cancer in the irritated area, but there is no corresponding increase in the total incidence; furthermore, this increased irritation leads actually to a decrease in the incidence of cancer in other organs. In persons engaged in alcoholic trades (barmen, waiters and brewers) there is a lower mortality from cancer of the lip than in others of their social group, but there are very high rates of mortality for cancer in all other sites, and an unusually high total rate. Contrasted with these, Peller noted that in cotton spinners, gas stokers and chimney sweeps there is a high mortality from cancer of the skin, but low mortality from cancer of the lip, esophagus and tongue. In this group, however, the total rate is also higher than in the social classes with which it is compared. Thus it was observed that in occupations having the lowest total cancer mortality, there was actually a higher mortality from cancer of the skin, when the workers were divided into two groups and compared with others of their social class.

Largely on the basis of these occupational statistics, Peller postulated that the production of a primary tumor in one organ produces immunity against tumors in other organs. If this can be regarded as proved, then his thesis is logical. Thus, it might be possible, by provoking cancer of the skin (applying light rays to a suitable area) to reduce the total number of inaccessible cancers. Subsequently, Peller and Stephenson (2) reached similar conclusions in a study of cancer in the United States Navy. They noted that among these naval men the rate for skin and lip cancer was higher than normal, but the rate for cancers at other sites was greatly diminished.

In his book on cancer in man Peller (3) further elaborates on his thesis that "cancer in one organ shields other organs to a considerable extent." He states that "a cured cancer leaves an increased resistance to the development of another primary tumor in some other part of the body." These statements are not paraphrased but are quoted verbatim because the possible implications are so im-

mense. He proposes to change the distribution of cancer, *i.e.*, replace cancers of high fatality by cancers of low fatality. Since the neoplasm of lowest fatality is cancer of the skin, he suggests *provoking* this cancer, probably by exposure to actinic or ultraviolet rays. "A systematically planned policy of increasing skin cancer incidence in early manhood may succeed in a far more intensive reduction of cancer mortality." He further states that, "it is within our grasp to change the organ distribution of cancer in about 90% of all cases, and to influence the distribution of cancer to a considerable extent. It is therefore feasible by this method to save from death almost 90% of cancer victims." Conrad and Hill (16) felt that Peller's conclusions were interesting and important and that the occupational mortality statistics of England and Wales (used by Peller (2)) should be studied in greater detail.

In a study of mortality rates by social class, Conrad and Hill (16) found that as the social level declines, cancer of the tongue and stomach as well as of the skin and lip, rises steadily. The highest social class, which has the lowest rates for skin and lip cancer, also has the lowest rates for all other sites. The lowest class (unskilled workers) has the highest rates for cancer of the skin and lip, and also has the highest rates for cancer in other sites. These authors then made a comparison of the mortality from variously located cancers of each occupational group within its own social class, in order to test Peller's conclusions. In the various occupations of the highest social class, they failed to find the inverse relationship between the mortality from skin cancer and general cancer mortality. In the occupations of the second highest social class, they also noted very little association between the two rates. In the middle social class (largely skilled workers) there was a direct association between mortality from cancer of the skin and lip and mortality from cancer of the stomach. However, in studying the various occupations within this social group, there were some interesting findings. The earthenware workers, waiters and bookbinders had no deaths from skin cancer but had a higher number than expected from cancer at other sites. In plasterers and painters there was a normal incidence of skin and lip cancer for their social class. However, among plasterers the incidence of cancer of the stomach (and possibly of the tongue) was high, whereas among painters it was normal for lip and skin cancer but below normal for cancer of the tongue, esophagus and other organs, with the exception of the stomach; at the latter site, the rate was higher than expected. In general, these authors felt that there was no inverse relationship between skin cancer and cancer at other sites in occupations involving workers of the middle social class.

In occupations involving workers of the next to the lowest social group, there was some inverse relationship on the whole, but this was not borne out in detailed examination of the data for the occupations concerned. However, Conrad and Hill noted that agricultural laborers have a somewhat higher mortality from skin and lip cancer but a very low death rate from cancer at other sites. Drivers of horsedrawn vehicles have a slightly high mortality from skin and lip cancer and a very high rate from cancer at other sites. Gas stokers and boatmen have a high rate for cancer of the skin and lip, and both groups have a very high rate

for cancer at other sites. Workers in the alcohol industry (*e.g.*, barmen, cellarmen and brewers of ale and stout) do not die from skin or lip cancer, but the mortality rate is substantially above normal for cancer at other sites.

In the occupations involving workers of the lowest social class (various categories of laborers), the largest group had a high mortality rate from cancer of the skin and lip, and also a high rate from cancer at other sites.

Conrad and Hill concluded that examination of occupations in relation to the social class of the workers did not reveal any inverse relationship between the mortality from skin and lip cancer and cancer at other sites. On the contrary (with exceptions), a slight direct association was noted, *i.e.*, in occupations in which there is a relatively high mortality from skin and lip cancer, there is also a high mortality from cancer at other sites.

In his book (3), Peller discounts the work of Warren and his associates as inadequately controlled and therefore inconclusive. He is also critical of the 1937–1939 and 1948–1949 surveys of the Public Health Service. Simpson (17), in reviewing Peller's book, stated that it is provocative and could become one of the most controversial books in the field of oncology. However, although Simpson found it stimulating, he did not find it convincing. Only a biostatistician could resolve the findings of Peller and of Warren and others. Since the concept is obviously very important, this should be attempted.

In reviewing the literature, Schreiner and Wehr (18) were impressed with the infrequency of references to multiple cancers involving the skin concomitant with lesions involving the internal organs. They believe that the answer lies in the probability that the skin lesions had been removed surgically or had been healed by radiation, and autopsy records did not take this into consideration.

During a twenty-year period, Schreiner and Wehr noted 85 cases of primary multiple basal-cell epitheliomas of the skin. Nine of the patients had, in addition, other primary malignant neoplasms, such as retroperitoneal lymphosarcoma, malignant papilloma involving the bladder, and malignant tumor of the kidney. Twenty-six cases of multiple primary pearl-forming epithelioma of the skin were seen, and 56 cases of multiple cancer of the skin, with basal-cell and pearl-cell epitheliomas were found in the same patient. Three of these patients had, in addition, primary malignant growths in other organs.

In 2,502 cases of cancer of the lung observed by Cahan (19) at Memorial Center, New York, over a period of twenty-eight years, there were 81 instances in which the lung tumor was one of two or more separate primary lesions—an incidence of 3.2 per cent. Cahan (19) considers tumors to be synchronous if the time interval between the establishment of the first and second primary lesions is less than six months, and metachronous if this time interval is more than six months. This is an arbitrary division, since in certain instances it might conceivably take more than six months to establish a diagnosis of the second primary lesion. In his series, the lung cancer was synchronous with another malignant tumor in 24 instances, and metachronous in 40 instances. In 4 of the 40 metachronous cancers, lung cancer appeared first, the time interval between the first and the second growths ranging from six months to four and a half years. There were 17 instances of basal-cell carcinoma of the skin, associated with lung cancer.

The 17 basal-cell skin cancers are deserving of special mention. Ten of them were synchronous with the carcinoma of the lung. The other 7 preceded the carcinoma of the lung by five months, one year, two years, seven years, eight years, ten years and twenty-eight years, respectively. The basal-cell growths involved the skin of the lip, eyelid, neck, cheek, nose and axillary regions. These cases should be a test for Peller's hypothesis. Another interesting finding in this series was the occurrence of cancer in the head and neck region in 36 patients. Eighteen of these cancers were in the oral cavity, and 18 were in the extrinsic and intrinsic larynx. A common etiologic factor was suspected.

Cahan came to the following conclusions from this survey:

1. In every patient with a known malignant tumor, a special watch should be kept for the possible occurrence of a second primary tumor.

2. Every so-called solitary lesion occurring in the lung of a patient with a previously removed tumor should be considered as a second primary tumor, unless this diagnosis can be disproved. There is a 3½ to 1 chance that a solitary pulmonary shadow is a second primary tumor rather than a metastasis.

3. A nodule in the lung should not deter radical surgical removal of the other lesion, or in fact of either lesion.

4. The striking association between carcinomas of the head and neck and separate primary lesions in the lung should lead to a search for one or the other whenever either is diagnosed.

III. CONCLUSIONS

As a case can be made for predisposition to cancer in certain persons, it is mandatory that, in the follow-up study, the physician carefully screen cancer patients for the possibility of a second primary tumor. This is especially true in view of the increasing rate of recovery following surgical treatment of the initial cancer.

By the same token, aggressive treatment by the surgeon of each new primary lesion may result in a startling increase in longevity in the occasional patient.

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NEEDS FOR RESEARCH IN GERONTOLOGY AND THEIR IMPLICATIONS FOR THE PHYSICAL MEDICINE AND REHABILITATION SERVICE*

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Despite the constant presence of old people from the dawn of time, we have not solved the biologic enigmas of aging. We do not cure the so-called irreversible changes in aging tissues and minds, nor do we seem to be satisfactorily successful in the prevention or delay of such changes. During the past fifty-six years or so, new drugs, preventive medicine, sanitation, and sanitary engineering have increased mass longevity to the extent of almost twenty years among younger people. In the sixth, seventh and eighth decades of life there has not been as much change, except that there are more oldsters, and that after the age of 45 about 1 out of 4 of them is disabled and sick—a morbidity rate which increases to 1 out of 2 after the age of 80. It appears that a further increase in absolute and relative numbers is ahead of us, because medical science is prolonging the lives of the sick and disabled.

MEDICAL ASPECTS

In a comparative sense there is much research regarding the endocrinology of aging, and the cardiovascular, neurologic and psychiatric disorders. The neoplastic diseases of all ages are being attacked from all sides by researchers, but early surgical extirpation of the neoplasm still seems to be the most successful treatment, with radiologic methods next in value. Chemotherapy has not accomplished much as yet. The nuclear physicists and the biochemists have teamed up on this problem. Less than a month ago there was a conference of psychologists at the M. D. Anderson Hospital concerning the relationships of stress (1) and human cancer. This is not so esoteric as it might seem, considering what we already know about psychosomatic functions and endocrinology. Everybody engaged in research is still groping for increased knowledge in the field of malignancy.

There is a great lack in total knowledge of diseases of the nervous system which, like cancer, affect more people because of longer survival. If not neoplastic, they usually result from some form of degeneration in the nerve cells or the vascular supply. Apparently these degenerative diseases of the nervous elements are caused by some fault of nutrition (due to either a toxic factor or a deficiency), because tissue cultures in which cellular nutrition is constantly good seem to be able to live forever. Other studies of nutrition may sooner or later provide data which will lead to more rapid healing and longer life, thereby multiplying the associated gerontologic social problems.

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Mental ill health is also a tremendous problem of aging. A great deal of research has been going on, but there is still much room for further investigation. Communist "brain-washers" deliberately reversed therapeutic psychology and psychiatry, as a military weapon and a political device. People, particularly the negative thinkers and dependent-minded, have a penchant for letting challenges of society crowd them into mentally unhygienic attitudes and mental illnesses, and being "brain-washed." There is need for more investigation to determine the point of no return for these people, to ascertain the various earlier stages, and to use what we already know about reversing the "functional" cases toward normal more quickly and more efficiently. If the results of these researches are more successful than at present, many more oldsters will be enabled to live in the society outside mental hospitals and nursing homes.

The full gamut of effective preventive measures against the stresses of life before degenerative diseases supervene is only being suspected now. Thirty years ago "psychosomatology" was not a well-known word, even among practicing physicians. Now the average lay citizen recognizes Selye's General Adaptation Syndrome (1) by attributing his own peptic "ulcer" symptoms to the stresses and frustrations he brings upon himself or cannot avoid. What drugs will eventually be taken, or what protective food additives will be used for something as well-known as gastric ulcers? The ataractic drugs have many interesting effects psychosomatically. Perhaps the removal of toxins from the patient's total dietary intake will aid in social adjustments.

The inheritance of biologic vulnerabilities may not be entirely interpreted as familial predispositions when more information is obtained about environmental effects impressed upon individuals as combined vectoral results of food, family, "mores," infections, and traumata of body, mind, tissue and thought. However, successes in research which could be put into practical use to prevent disabilities associated with aging could do little for a whole generation to lift the load of predictable rehabilitation needs; in fact, the rehabilitative burden would be even greater because of possibilities in the treatment of the more difficult cases.

In all too many diseases the etiology is unknown or obscure, *e.g.*, cirrhosis of the liver, and the collagen group disorders. These are formidable research challenges in gerontology, because the geriatric patient apparently acquires no immunity toward them. Some men and women with these organic diseases resist them better and longer with good medical care administered early. If the will to recover remains, there is some service which the rehabilitation specialist can render by estimating individual physical reserves and assisting in developing unused substitutive capabilities.

SOCIAL AND ECONOMIC ASPECTS

Thus far in this consideration, the needs for research in the social and economic aspects of becoming aged have not been emphasized. Socially sympathetic thinkers have sloganized: If we insist on adding years to life, we should also add good living to those extra years. We are floundering as a nation between the

extremes of starkly callous "rugged individualism" and rather maudlin do-gooder socialism. In the social security plans of the government and industry the proper ages for retirement of men and women, and problems of disability and old age are still unsettled. These matters are compounding so quickly on the present surprised oldsters, who scoffed about it when ten years younger, that it may require a few more decade-increments of new lay gerontologists (voters over 65) before more realistic pronouncements are made regarding retirement and rehabilitation.

Already there are about 600,000 veterans 65 years of age or older, and these will be 1,700,000 in only four years. There is good reason to expect that most of them will live beyond the present male life expectancy of about 67.2 years. Thus, in five more years, when the majority of World War I veterans will be 65 or older, the gerontologic problems of the Veterans Administration will be greatly increased. The Department of Medicine and Surgery will have many more patients who have to be shifted to "intermediate" beds, as the present 9,000 intermediate patients of the Veterans Administration may be tripled or quadrupled. Either that, or by a change of philosophy which the public may demand, there will be as intensive medical care and rehabilitation as undermanned facilities can render. There may be future "crash programs" if something definitively realistic is not accomplished within two years.

At present the public, represented by the Congressional mind, is expecting good medical care, research and rehabilitation, and no relegating of "intermediates" to second-class care while the Veterans Administration is responsible for them. These are flies in the three ointments.

The funds will be too little and too late for timely development of the newer philosophy of geriatric medical care, which costs the full price of sincerely motivated staffing and well equipped hospital wards for diagnosis and treatment. Research cannot be just pulled out of the air. Scientists and technicians have to be trained, motivated and attracted, in spite of relatively poor pay, to the problems of the Veterans Administration, which are costly in time, effort and materials. Competent rehabilitation specialists with their paramedical assistants have been just as hard, if not harder, to train or acquire than the other medical personnel.

I can predict that the philosophy of treatment of "intermediate" patients will change, for it is changing or has changed already at the hospital level. Congress will respond when it understands. Congress served notice that it expects more gerontologic research when it raised the Bureau of the Budget's Veterans Administration medical research estimates by 65 per cent, and earmarked its appropriation in committee discussions for that purpose in June 1956.

Another department to be put under pressure will be the Physical Medicine and Rehabilitation Service. President Eisenhower's administration has already set a goal of 200,000 successful rehabilitations each year, and Congress has given components of the Department of Health, Education and Welfare the funds to increase training and facilities to reach that goal. When we actually reach that goal, it will be too low, but it will be much more realistic than the previous

national standards. It requires more than five years to produce a finished physiatrist, and just as many years to make a trained therapist of a high school graduate. The Physical Medicine and Rehabilitation Service will be in competitive position to perform its job in five years, only if it can be put into high gear for training and kept there by planners in the various offices in Washington.

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INFLUENCE OF THE ARYLSULFONYLUREAS ON THYROID FUNCTION IN OLDER DIABETIC MEN AND WOMEN

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Early in 1955, two German workers (1) described the blood sugar-lowering effect of a sulfonamide compound, N-p-amino-benzene-sulfonyl-N′-n-butyl urea (carbutamide), and the salutary action of this material in cases of diabetes mellitus. Shortly thereafter, two American workers (2) described the hypoglycemic action of a closely related compound, N-toluene-sulfonyl-N′-n-butyl urea (tolbutamide).

Both of the foregoing compounds have now been extensively employed for relatively short periods of time in the management of diabetes mellitus. In effective dosages the toxicity has been low, although recently a number of serious reactions have been associated with the use of carbutamide (3). The effectiveness of these drugs by mouth has stimulated their widespread application to the treatment of diabetes mellitus on an investigative basis. If found helpful, their long continued use is to be expected. In view of this, and the fact that carbutamide is a sulfonamide and that tolbutamide is closely related chemically, the investigation of their influence upon thyroid function in man has seemed to be important.

We have been unable to find any written report of the influence of these two sulfonylureas upon the human thyroid gland. However, Kirtley (4) recently stated that in continuing doses of 1 gram daily he saw no evidence for a suppressive effect of carbutamide upon the thyroid. Irwin (5) found that in doses up to 1.5 grams daily for several months, the thyroidal uptake of radioiodine was not affected by this drug. On the other hand, several workers (6–8) have reported that carbutamide in large doses for short periods of time suppresses iodine uptake by the thyroid, whereas tolbutamide in similar amounts does not.

Recently Larson (9) and Anderson (10) showed a marked goitrogenic effect in rats from the administration of carbutamide. Larson also studied the thyroids of animals receiving tolbutamide without observing hypertrophy or hyperplasia.

In view of the long-term usage which may be accorded these sulfonylureas if they are released for general medical usage, it has seemed wise to study not only the action of large amounts for short periods of time, but also the long-range effects upon the human thyroid associated with the use of optimal and maximal therapeutic doses.

With these points in mind, we studied thyroid function before and during treatment with carbutamide and tolbutamide by serial determinations of the basal metabolic rate, serum protein-bound iodine level, and thyroidal I^{131} uptake.

* Wakefield Memorial Fund Fellow.

Further, all patients undergoing treatment with either of these compounds were watched for clinical symptoms or signs of hypothyroidism.

SUBJECTS AND PROCEDURE

Fifty-five patients with diabetes mellitus were chosen for this study from the wards of the Bird S. Coler Hospital. There were 23 men and 32 women, ranging in age from 57 to 91 years with an average age of 73.4 years.

The ages of the 32 subjects who received tolbutamide, ranged from 57 to 89 years, with an average of 72.5. Corresponding figures for the 28 subjects who received carbutamide were 57 to 91 years, with an average of 71.2.

All subjects had been on the wards of the hospital for not less than six months prior to initiation of the study and had been under the care of the same attending and resident staffs for not less than three months immediately preceding their participation in the present program.

The known duration of diabetes in these subjects varied from three months to thirty-eight years, with an average of 12.4 years. They had used insulin for periods ranging from four weeks to approximately thirty-five years, with an average of 8.8 years.

In none of these subjects was the diabetes mellitus completely controlled when therapy with the arylsufonylureas was begun, and all but 3 of them were receiving insulin. Only 1 subject could be considered to be of the "brittle" type. The others were of the "adult" or "stable" type and the diabetes could be easily controlled on a measured diet and appropriate doses of insulin. Five subjects received first one and then the other of the two sulfonylureas.

Twenty-eight patients were first given tolbutamide; later 4 of these were also treated with carbutamide. Twenty-seven subjects first received carbutamide; in 1 of them, because of a moderately severe generalized urticarial-febrile reaction, therapy was changed to tolbutamide on the fifteenth day of treatment without further mishap.

As criteria of thyroid function, the general condition of the patient, the level of the serum protein-bound iodine, the basal metabolic rate, and the thyroidal uptake of radioiodine were employed. The determinations of serum protein-bound iodine were made by the method of O'Neal and Simms (11). The basal metabolic rates were obtained under standard conditions, using a Benedict-Roth metabolimeter. Uptake gradients after single doses of the arylsulfonylureas were measured according to the method of Stanley and Astwood (12). In the more prolonged studies, thyroidal I^{131} uptake was determined by direct counting over the gland with a Geiger-Mueller tube, and urinary excretion was measured by means of a scintillation well counter.

No single tracer dose of I^{131} exceeded 25 microcuries, and in no subject did the total dose exceed 100 microcuries spread over a forty-week period. Most of the subjects had only three determinations of thyroidal radioactive iodine uptake—none at less than three-week intervals. In the case of the subjects given the arylsulfonylureas in dosages of 3 or 4 grams daily for four days, the initial esti-

mation of thyroidal I^{131} uptake was made three weeks prior to the period of treatment, and the second estimation was made on the fourth day of administration.

The usual clinical criteria for detecting underfunction of the thyroid were kept in mind in appraising the over-all clinical status of each patient.

RESULTS AND COMMENTS

From a clinical standpoint, none of the subjects appeared to be hypothyroid at any time during the course of therapy, whether taking carbutamide or tolbutamide.

A. *The basal metabolic rate*

The basal metabolic rate was determined in most of the subjects one or more times prior to, and again during therapy with the arylsulfonylureas, using the Du Bois standards (13).

In 10 subjects receiving 1 gram of carbutamide daily and in 9 receiving 1 gram of tolbutamide daily, the average pre-treatment basal metabolic rates were +5 and +3 per cent, respectively, with ranges of −12 to +18 and −10 to +12 per cent, respectively (Fig. 1). Corresponding values during or near the end of the therapeutic period were +7 and +5 per cent, respectively, with ranges of −8 to +17 and −8 to +18 per cent, respectively (Fig. 1). No significant changes

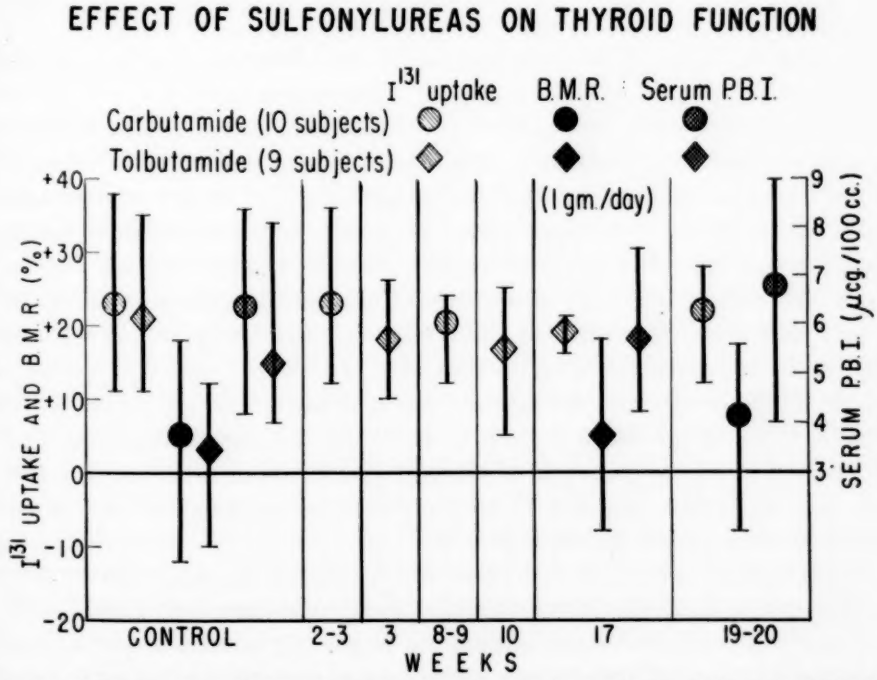

FIG. 1. Effect on thyroid function of sulfonylureas in a dosage of 1 gram daily in diabetic subjects. The center of the identifying circle or square represents the average value for all determinations. The vertical line represents the range of values.

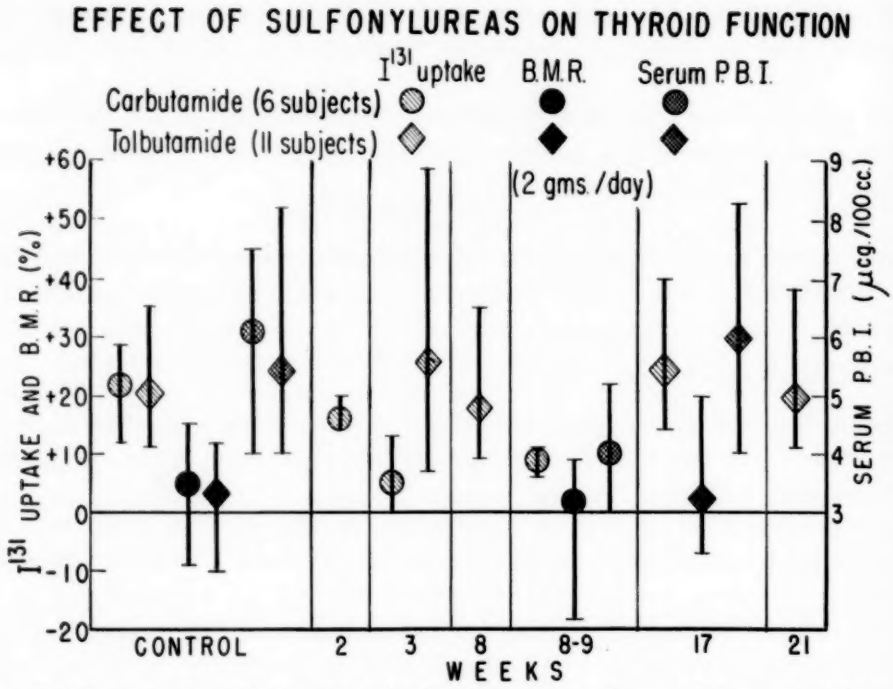

FIG. 2. Effect on thyroid function of sulfonylureas in a dosage of 2 grams daily in diabetic subjects. (For further explanation of symbols, *see* legend to Figure 1.)

from control values could be observed under the influence of either drug in this dosage.

Six subjects received carbutamide in a dosage of 2 grams daily. Before treatment the average basal metabolic rate was +4 per cent (range, −9 to +15). After eight to nine weeks of therapy the average rate was +2 per cent (range, −18 to +9) (Fig. 2). There was a suggestion of lowered levels as a result of treatment, although in only 2 of the subjects did the basal metabolic rate fall below −10 per cent (the usually accepted lower limit of normal). However, none of the subjects had such a low rate prior to the treatment. For the group as a whole, the changes were not statistically significant (Fig. 2).

Eleven subjects received tolbutamide in a dosage of 2 grams daily. Before treatment the average basal metabolic rate was +3 per cent (range, −10 to +12). In the seventeenth week of therapy the average rate was +2 per cent (range, −7 to +20) (Fig. 2). Thus there was no appreciable change during tolbutamide therapy in this dosage.

It would appear, therefore, that there was no significant alteration in the basal metabolic rate as a result of the administration of either drug in a dosage of 1 gram daily for periods of time ranging up to twenty weeks. When a dosage of 2 grams daily was used, there was a suggestion of a trend toward lowering of the basal metabolism when carbutamide was administered for nine weeks, whereas there was no similar trend when tolbutamide was administered for as long as seventeen weeks (Fig. 2).

B. *Serum protein-bound iodine level*

When either drug was used in a dosage of 1 gram daily over periods ranging from three to twenty weeks, there was no significant change in the concentration of serum protein-bound iodine (Fig. 1).

Six subjects received carbutamide in a dosage of 2 grams daily for periods up to nine weeks. During therapy there was a decrease in the level of serum protein-bound iodine from an average control value of 6.1 micrograms per 100 cc. (range, 4.0 to 7.5 micrograms) to an average treatment value of 4.0 micrograms per 100 cc. (range, 3.0 to 5.2 micrograms) (Fig. 2). In only 1 of the 6 subjects was there a change to a definitely low value during therapy (from 6.2 to 3.0 micrograms per 100 cc.). In 1 other patient there was a drop from a control level of 8.1 micrograms to a treatment level of 4.4 micrograms per 100 cc. A downward trend during therapy is suggested by these data, but as only 6 subjects were involved and the individual variations were great, the results were not statistically significant.

Eleven patients received tolbutamide in a dosage of 2 grams daily for periods up to seventeen weeks. Before treatment, the level of serum protein-bound iodine was 5.3 micrograms per 100 cc. (range, 4.2 to 8.2 micrograms). During therapy the values remained about the same, the average being 6.0 micrograms per 100 cc. (range, 4.0 to 8.3 micrograms) (Fig. 2).

C. *Thyroidal uptake of radioiodine* (I^{131})

Two diabetic subjects each were given a single oral dose of 4 grams of carbutamide, and 2 additional diabetics were each given similar oral doses of tolbutamide. An uptake gradient for I^{131} was established according to the method of Stanley and Astwood (12). Changes in the gradient were plotted as counts per minute against the square root of time. In 1 of the 2 diabetics given carbutamide there was only slight inhibition of radioiodine uptake, but in the other subject there was almost complete inhibition for twenty-four hours. In the 2 subjects given tolbutamide, there was no change in the gradient in 1, and only slight inhibition in the other. It was concluded that in some diabetics, carbutamide is capable of inhibiting thyroidal radioiodine uptake to a marked degree, whereas under the same conditions tolbutamide may have very little if any effect in this direction.

Carbutamide and tolbutamide were then each given in a daily dosage of 4 grams for four days to each of 6 subjects (Fig. 3). The thyroidal radioiodine uptake was determined before, and at the end of the period. In the 4-gram carbutamide series the average pre-treatment uptake was 23.3 per cent (range, 12 to 31 per cent); during treatment the uptake was 5.3 per cent (range, 2 to 10 per cent). These changes were statistically significant, with a P value of less than 0.001. In the tolbutamide series the average pre-treatment uptake was 19.3 per cent (range, 8 to 30 per cent); during treatment the average uptake was 16.5 per cent (range, 7 to 26 per cent). None of these changes was significant within the 5 per cent level of confidence.

Following this study, 3 subjects were given carbutamide in a dosage of 3 grams

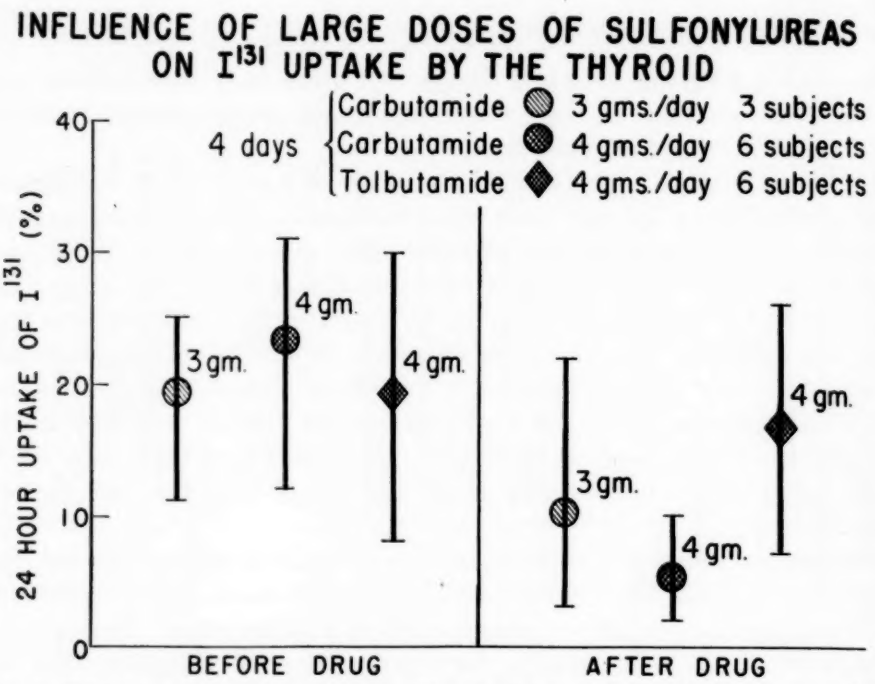

FIG. 3. Effect on thyroid function of sulfonylureas in dosages of 3 or 4 grams daily for four days in diabetic subjects. The pre-treatment values were obtained twenty-two days before the drug was administered. Although the range of values with the 3-gram dosage of carbutamide was wide, in each instance the value after treatment was lower than that before treatment. (For further explanation of symbols, *see* legend to Figure 1.)

daily for four days, and the radioiodine uptakes determined before and after therapy (Fig. 3). Before treatment the average level of uptake was 19.3 per cent (range, 11 to 25 per cent); during treatment the average uptake was 10.3 per cent (range, 3 to 22 per cent). In each instance treatment value was lower than the pre-treatment value. The average treatment uptake decreased to 47 per cent of the control figure. No attempt was made to calculate a P value, because the value for n was so small.

Ten subjects receiving carbutamide and 9 receiving tolbutamide were given continuing doses of 1.0 gram daily for periods up to twenty-one weeks, during which time the thyroidal uptake of I^{131} was determined on two to four occasions. In Figure 1 it may be seen that the thyroidal radioiodine uptake was not significantly altered by the administration of either drug. This statement also applies to the continuing use of tolbutamide in 11 subjects at a dosage level of 2.0 grams daily for up to twenty-one weeks (Fig. 2). In the latter instance the pre-treatment average uptake was 22.1 per cent (range, 11 to 36 per cent). Near the end of therapy the average uptake was 19.5 per cent (range, 11 to 38 per cent) (Fig. 2). The story was somewhat different when carbutamide was given in a dosage of 2.0 grams daily to 6 subjects for periods of time up to twenty weeks (Fig. 2). The control value was 21.6 per cent (range, 12 to 28 per cent). The treat-

ment value was 8.7 per cent (range, 6 to 11 per cent). These changes are well within the 5 per cent level of confidence.

SUMMARY AND CONCLUSIONS

Thyroid function was studied in 55 elderly patients with diabetes mellitus before and during treatment with the sulfonylureas, carbutamide and tolbutamide.

No clear-cut clinical evidence of hypothyroidism was observed in any patient at any level of dosage used.

There was a suggestion of a decrease in the basal metabolic rate and the level of serum protein-bound iodine when carbutamide was used in a dosage of 2 grams daily for relatively long periods of time (up to twenty weeks). No change was observed during similar treatment with tolbutamide.

Large dosages of carbutamide (3 and 4 grams of daily) for four days depressed the uptake of radioiodine by the thyroid gland. No change in uptake was observed when tolbutamide was used in similar dosage for the same length of time.

The long continued use of either sulfonylurea in a dosage of 1 gram daily was not associated with any appreciable change in the thyroidal uptake of radioiodine. However, in the case of carbutamide, when the dosage was increased to 2 grams daily, there was a statistically significant depression of the radiodine uptake.

It is concluded that dosages of carbutamide amounting to 2.0 or more grams daily should not be used for their hypoglycemic action over long periods of time, because of the concomitantly depressed state of thyroidal iodine uptake. No similar action was demonstrated for tolbutamide, but the effect of this drug on thyroid function should be studied for much longer periods of time before employing it routinely as an agent in the prolonged treatment of diabetes mellitus.

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Abstracts of Current Literature

ACETYL-DIGITOXIN. A CLINICAL STUDY.

Bernstein, A.; Kogan, E., and Cohen, I. E. *Journal-Lancet* **76:** 228 (Aug.) 1956.

Acetyl-digitoxin, a pure crystalline glycoside derived from *Digitalis lanata*, was administered to 12 patients with acute cardiac failure. Their average age was 53.8 years. The majority of the patients were digitalized for the first time. The dosage was 0.4 mg. orally every six hours repeated until toxicity developed or the patients had received 6.4 mg. Then the drug was discontinued for three days. Following this, another 6.4-mg. dose was given in a similar manner, a two-day interval allowed, and then the drug administered in a third trial. If toxicity appeared during any trial, the drug was discontinued until the toxic or electrocardiographic signs disappeared and then was administered again until all three trials had been completed. Adequate digitalization was secured in 11 patients. Failure in 1 patient was due to long-standing heart disease complicated by pulmonary emboli. The average digitalizing dose was 1.6 mg. of acetyl-digitoxin, indicating excellent absorption from the gastro-intestinal tract. The average toxic dose was 4.5 mg. Two patients tolerated 6.4 mg. without side-effects. The ratio of the digitalizing dose to the toxic dose was 37 per cent, suggesting that a wide margin of safety exists in the pharmacologic action of acetyl-digitoxin. Toxic symptoms were dissipated in twenty-four to forty-eight hours after discontinuing the drug. Another advantage of the preparation was the fact that nausea and vomiting usually preceded toxic effects on the myocardium. Acetyl-digitoxin is excreted much more rapidly than digitoxin. It is excreted less rapidly than lanatoside C, however, because digitalization was maintained in all patients during the interval of rest between trials. Because of the wide range of safety and the rapid rate of dissipation, acetyl-digitoxin should replace digitoxin in the treatment of congestive heart failure.

ORAL DIBENYLINE IN DISTAL SENILE OBLITERATIVE ARTERITIS.

Boyd, A. M. *Lancet* **26:** 869 (Oct. 27) 1956.

A fundamental error in administering vasodilators to patients with obliterative arterial disease is the failure to recognize that intermittent claudication, ischemia, and gangrene result from numerous underlying causes among which may be infection. The degree of arterial obstruction will determine the effect of a vasodilator. The distal type of obliterative arteritis that is seen chiefly in the elderly may be expected to respond. Here the arteriosclerotic changes are limited mainly to the periphery. Chronic ischemia is confined to the extremities. Local exacerbations lead to episodes of superficial gangrene. Sympathectomy is the most successful type of therapy but is not always desirable in elderly patients. Therefore, a trial of Dibenyline, the action of which is exerted on the periphery and is long lasting, was undertaken. Seventeen patients with mild obliterative arteritis and 13 whose disease was classified as moderate received Dibenyline in dosages gradually increased from one 10-mg. capsule at bedtime to one capsule three times daily. A few patients received 60 mg. daily. Severe cases are now treated with Dibenyline administered intra-arterially but the results of this treatment are not included in this report. Results of the oral therapy were evaluated on the basis of clinical observations. Good results were obtained in 12 of 17 mild cases and in 6 of 13 moderate cases. These patients were followed for six months or longer. The best results were obtained in patients whose extremities were least obstructed. Coldness and numbness of the hands and feet disappeared. Raynaud's phenomenon was either relieved or the frequency of attacks diminished. Treatment was unsuccessful in 2 patients, and was discontinued after nine days in another because of nausea. Other unwanted effects included dizziness, 5; drowsiness, 4; and nasal stuffiness,

4. Treatment was discontinued after eleven months in 1 patient, who had improved, because of depression, although it could not be determined whether this was due to the drug. Dibenyline is concluded to be the preferred treatment in mild cases of obliterative arteritis and to offer an alternative to sympathectomy in moderate cases.

A CLINICAL STUDY OF PULMONARY EMBOLISM.

DeLaughter, G. D., and Anlyan, W. G. *Surg., Gynec. & Obst.* **103:** 695 (Dec.) 1956.

During a 6.5-year period, 60 cases of pulmonary embolism were treated and followed. The average age of the patients was 47.4 years, and the oldest patient 77 years of age. The emboli occurred as follows in the numbers of patients listed: multiple, 13; postoperative, 38, associated with malignancy, 2; associated with trauma, 7; idiopathic, 13. Conditions frequently associated with pulmonary embolism were: a previous history of embolism, extensive varicosities of the legs, congestive heart failure, extensive pulmonary or abdominal surgery, obesity, age beyond 50 years, extensive trauma to the legs, immobilization, and polycythemia vera. Five cases of embolism that occurred while the patient was receiving anticoagulant therapy are presented in detail. Half of the 60 patients had no physical signs of peripheral venous thrombosis, emboli in these cases being assumed to have arisen from the pelvis. Twenty patients had signs of venous thrombosis in the extremities, and 10 had bilateral venous thrombosis. The symptoms in the numbers of patients indicated were: calf tenderness, 20; leg pain, 16; Homan's sign, 12; leg swelling, 9; groin tenderness, 8; pretibial vein dilatation, 1; The difficulty in diagnosing pulmonary embolism is stressed. Most patients initially have symptoms referable to the chest that may be designated a pain, a catch, a tight feeling, fullness, inability to breathe deeply, or shortness of breath. Roentgenograms may aid an early diagnosis but have seldom proved conclusive. Electrocardiograms have helped to rule out myocardial infarction but have been of little immediate help in diagnosing pulmonary embolism. A patient in whom signs indicate venous thrombosis or pulmonary embolism should be treated with anticoagulant therapy. The authors' method —giving heparin for at least four days and following it with the administration of Dicumarol —is outlined. They believe that the patient should receive anticoagulant drugs for twenty-one days and longer if there are signs of severe or deep venous thrombosis. Antibiotics are used routinely. After four days, the patient is ambulatory, with elastic bandages on the knees. Sitting or standing is discouraged, while elevation of the feet and walking are encouraged. The primary contraindications to this mode of therapy consist principally of progressive thrombosis or major hemorrhage occurring during the administration of anticoagulants, and pulmonary embolism following prostatic resection. Suppurative pelvic thrombophlebitis and the need for protection from pulmonary embolism in the face of progressive thrombosis or major hemorrhage are indications for ligation of the vena cava. Pulmonary embolism after prostatic surgery should also be treated by inferior vena cava ligation. Anticoagulant therapy was employed in each of the patients reported except 2 who required ligation of the inferior vena cava. It prevented further embolism in 50 of 57 patients and fatal embolism in all except 3. One patient died during the interruption of therapy because of profuse prostatic bleeding. As experience with this therapy is gained, there appears to be less controversy as to its preference.

CORTISON UND PREDNISON IN DER BEHANDLUNG DER HEMIPLEGIE (CORTISONE AND PREDNISONE IN THE TREATMENT OF HEMIPLEGIA).

Gianoli, A. C. *Schweiz. med. Wchnschr.* **86:** 1025, 1956; through *Ciba Lit. Review* **1:** 342 (Dec.) 1956.

An adrenocortical hormone was administered to 22 patients with apoplectic hemiplegia. Some had shown no clear-cut improvement in motoricity in response to previous treatment, and others were depressed and apathetic and showed no interest in exercise therapy. The daily dosages, which were reduced as treatment proceeded, were initially 300 mg. for cor-

tisone and 60 mg. for prednisone. The duration of treatment varied between seven and eighty-nine days, with an average of five weeks. In 12 patients, the hormones had an astonishingly good effect upon the patient's psychic make-up and motor functions. In 3 patients, however, this result could not be ascribed with certainty to cortisone alone inasmuch as other drugs were also administered. In 3 patients, the effect of hormone therapy was not definite. The remaining 7 patients derived no benefit. Patients whose physical capacities had been impaired preceding apoplexy did not respond. No new attack occurred during treatment. The beneficial effect of this therapy in most cases is undoubtedly due to psychomotor stimulation of the patient. It is also possible that adrenocortical hormones exert a direct influence on the cerebral nerve cells or the condition of the muscles.

COMPARATIVE INVESTIGATIONS ON THE INFLUENCE OF CORTISONE AND PREDNISONE (M.S.D.) ON THE CONTENT OF SODIUM AND POTASSIUM IN SWEAT.

Grønbaek, P. *Acta rheum. scandinav.* **2:** 170 (Fasc. 3) 1956.

Using as a basis the finding by Conn *et al.* that the electrolyte concentration in thermal sweat is a reliable index to adrenocortical activity, the sodium/potassium ratio in thermal sweat produced under standard conditions was determined in 15 patients with rheumatoid arthritis before and after treatment with 15 mg. of prednisone daily for eight days. No significant change occurred during treatment in 13 patients. The ratio in 2 patients with diabetes mellitus was raised after treatment. Neither were there significant changes in the ratio after treatment with prednisone for a prolonged period. When cortisone was replaced by prednisone, 10 of 11 patients so treated showed an increased sodium/potassium ratio after replacement. The rise was significant in 5 patients. When prednisone was replaced by cortisone in 7 patients, the sodium/potassium ratio fell. The interpretations of these data are discussed. The author has previously demonstrated a correlation between the sodium/potassium ratio in sweat and increased activity of the adrenal cortex. If a fall in the ratio is tantamount to augmented adrenocortical activity, it can be concluded from this study that prednisone does not influence the electrolyte balance to the same extent as does cortisone.

NODULAR VASCULITIS. REPORT OF TWO CASES OF A PLAQUE TYPE ASSOCIATED WITH HYPERTENSION.

Irgang, S. *A.M.A. Arch. Dermat.* **74:** 245 (Sept.) 1956.

Reports are presented of 2 cases of a plaque type of nodular vasculitis that originated as such. These occurred in obese, hypertensive Negro women in the sixth decade of life. The eruption in both patients was confined to the legs. In one, the lesions were sparse and asymmetrical; in the other, they were relatively numerous and symmetrically distributed. Both patients had roentgenographic evidence of widened aortas and of osteoarthritis, and electrocardiographic indication of myocardial damage. Blood studies showed lymphocytosis. Histologically the cutaneous lesions appeared identical except for the additional involvement of the venules of the subcutis in the second patient. The principal histopathologic findings were noted in the subcutis and consisted of predominant thickening and fibrosis of the walls of the arterioles or of both arterioles and venules with decided narrowing of their lumina, the presence of fat necrosis in relation to the affected blood vessels, replacement of the major portion of fat cells by an intense fibrotic process, disorganization of part of the collagenous fibers, and the presence of a relatively sparse lymphocytic infiltrate about the small blood vessels.

RITALIN—A NEW AGENT FOR MILD DEPRESSIONS. A PRELIMINARY REPORT.

Jacobson, A. *M. Ann. District Columbia* **25:** 491 (Sept.) 1956.

Ritalin, methylphenidylacetate hydrochloride, was administered to 18 patients in the fifth, sixth and seventh decades of life who were undergoing psychotherapy for depression. Seventeen patients received placebo medication. Ritalin appeared to make the patient

better able to cooperate. An increase in alertness, dissipation of early morning depression and fatigue, and a sense of well being occurred in the drug-treated patients. No evidence of dependence appeared. The drug could be discontinued in all except 6 patients who required only half to two-thirds of the effective therapeutic dose for maintenance. No significant effects upon blood pressure or pulse rate were observed. When anxiety was a factor, the dosage of Ritalin was small, 10 to 30 mg. daily, because it had a tendency to intensify anxiety symptoms. In combination with an ataraxic drug, it proved valuable when there was anxiety. Ritalin counteracted the lethargy or oversedation caused by ataraxic drugs. Its use in a few tense, agitated schizophrenic patients proved disappointing. The effective dosage range in patients with depression varied between 30 and 120 mg. daily. In combination with ataraxic drugs, the dosage was 10 to 60 mg. The investigation of the use of Ritalin in such conditions as narcolepsy, epilepsy, postpartum depression, and various psychophysiologic disorders is suggested.

HARBITZ-MÜLLERS DISEASE AND THYROTOXICOSIS.

Jervell, A., and Ytrehus, Ø. *Acta med. scandinav.* **156** (Supplement 319): 33–37, 1956.

Case reports are presented for 2 women aged 52 and 57 years respectively, with Harbitz-Müllers disease, in whom moderately severe thyrotoxicosis developed. Both patients had elevated plasma cholesterol levels. Each had had angina pectoris for some time. Examination of the first patient showed signs of xanthomatosis with xanthelasmata on the upper eyelids, xanthoma tuberosa on the extensor tendons of three fingers corresponding to the metacarophalangeal joints, and xanthoma tuberosa on both elbows. This patient was treated with Lugol's solution, the intention being to keep her slightly thyrotoxic and to try to influence the hypercholesterolemia. Clinical symptoms regressed during treatment but recurred when therapy was interrupted on two occasions. The angina pectoris remained almost unchanged, and the xanthomata increased slightly during the observation period. No correlation could be found between the severity of the thyrotoxicosis and the hypercholesterolemia. The second patient had xanthoma tuberosa on both Achilles tendons. The disease was well controlled with thiouracil, but the xanthoma tuberosa remained unchanged. After eight months treatment, the plasma cholesterol level increased significantly and the angina became aggravated. Possible explanations offered for the different courses of the 2 patients are: 1) that the function of the thyroid was more restrained in the thiouracil-treated patient than in the one treated with iodine, or 2) possibly iodine and thiouracil may have different effects upon the plasma cholesterol level. Proper treatment of patients with Harbitz-Müllers disease and thyrotoxicosis appears to be to keep them slightly thyrotoxic, whether the treatment be medical or surgical. These patients must be carefully supervised for life, and with regular determinations of the plasma cholesterol level. It is the physician's task to avoid both thyrotoxicosis and hypercholesterolemia.

MITRAL STENOSIS IN PATIENTS OVER THE AGE OF SEVENTY.

Kløvstad, O. *Acta med. scandinav.* **156** (Supplement 319): 99–103, 1956.

Among 83 patients over the age of 71 years with mitral stenosis, 31 had combined mitral-aortic lesions. The exact valvular diagnosis was made post mortem in 9 of 21 with mitral lesions, and in 14 of 20 with combined mitral-aortic lesions. The female-male ratio was 4:1. A history of rheumatic infection existed in 43 per cent. Auricular fibrillation was present in 77 per cent with mitral lesions and in 61 per cent of those with combined mitral-aortic lesions. Thirty-seven per cent survived for more than ten years with heart failure. Systolic hypertension was more frequent (40 per cent) than hypertonia (13 per cent). Signs of coronary heart disease frequently occurred both clinically (47 per cent) and at necropsy (88 per cent). Heart failure was the cause of death in 39 per cent, embolism in 35 per cent. Coronary heart disease and aortic stenosis (sclerotic changes in rheumatic aortic lesions) increase with advancing age, sooner and more frequently in males. These heart lesions are

the main causes of heart failure in old age in general, and also most certainly in unrecognized or previous asymptomatic mitral stenosis. This may also explain the increasing female-male ratio in mitral stenosis in old age groups. Mitral stenosis in old age does not have any special clinical characteristics, but should be suspected when signs of coronary heart disease or aortic stenosis are combined with auricular fibrillation. The longevity of old women with mitral stenosis in particular may be explained by a slight and slow development of coronary heart disease, without which the mitral stenosis may be asymptomatic until death from causes unrelated to the rheumatic heart disease. (From author's summary and conclusions.)

CIRCULATORY STUDIES IN LIVER CIRRHOSIS.

Krook, H. *Acta med. scandinav.* **156** (Supplement 318): 1–160, 1956.

Among new experimental technics useful in the investigation of the hepatic vasculature are measurement of the portal pressure indirectly by hepatic vein catheterization and measurement of the hepatic blood flow by means of the disappearance-rate constant for colloidal radioactive gold from the circulation. An investigation was undertaken using the first of these methods in an attempt to compare the portal pressure recordings with clinical, laboratory and histologic findings. Sixty-four patients with cirrhosis of the liver were examined and the findings compared with those in 35 control patients and 38 with other liver diseases. The series included the following types of cirrhosis with the numbers of patients listed: alcoholic cirrhosis, 24; cryptogenetic cirrhosis, 22; post-hepatitis cirrhosis, 13; hemochromatosis, 3; cardiac cirrhosis, 2. The results of hepatic-vein catheterization in these patients were as follows: 1) determination of the occluded hepatic venous pressure (OHVP) appeared to be of diagnostic significance in cirrhosis of the liver; 2) the difference between the free hepatic venous pressure (FHVP) in the controls and in patients of the cirrhosis series was highly significant; 3) the difference in pressure between the OHVP and the FHVP was much higher in the cirrhosis series and provided a rough measure of hepatic vascular resistance; and 4) in general, portal hypertension in this series appeared clinically at an OHVP of 18 mm. Hg or more, that is, with symptoms such as esophageal varices, splenomegaly or ascites, which were fairly rare at OHVP levels below this limit. However, such symptoms were sometimes absent, even when portal hypertension was pronounced. It was concluded that hepatic vein catheterization permits good evaluation of the degree of portal hypertension, which often is not possible from the clinical signs and symptoms. The OHVP was higher in the presence of vascular spiders, the difference being highly significant. It also tended to be higher in cases with hepatomegaly. The serum albumin was abnormally low in the majority of cases and was lower in patients with ascites than in those without. A ratio was found between OHVP and a serum albumin concentration of 7.3 Gm. per 100 ml. as an approximate level above which ascites formation occurred. Since it appears that the development of ascites is dependent mainly upon the ratio between the portal tension and the serum albumin level, this should be taken into account in the evaluation of the possibility of establishing a portacaval shunt in order to provide relief of ascites in cirrhosis. Patients with a serum bilirubin concentration of 3 mg. per 100 ml. had a higher OHVP on the average than did patients with less pronounced jaundice, the difference being highly significant. Other laboratory studies included determination of alpha-globulin, beta-globulin, gamma globulin and serum alkaline phosphatase levels, the antistreptolysin titer, and the performance of serum flocculation tests. The OHVP increased in relation to the degree of fibrosis seen in biopsy specimens. Vascular spiders occurred more frequently in patients with severe fibrosis. There was no correlation between liver-cell damage and OHVP. In general, patients with pronounced cellular infiltration had a higher OHVP than those without. The results of OHVP determinations are also given for patients in a non-cirrhotic series with alcoholic fatty liver, acute hepatitis, congestive heart failure, obstructive jaundice without cirrhosis, malignant liver diseases, and prehepatic portal venous obstruction. The radioactive gold disappearance-rate constant (K) was lower in patients with cirrhosis than in control patients. However, in 6 cirrhotic patients the value lay within

normal limits. Patients with esophageal varices, vascular spiders, or advanced liver-cell damage had a lower K than those without. The disappearance rate of colloidal radioactive gold was concluded to furnish a useful relative measure of hepatic blood flow.

AN EVALUATION OF NICOTINYL SALICYLIC ACID IN ARTERIOSCLEROSIS OBLITERANS.
Kropf, W. *J. Mount Sinai Hosp.* **23:** 832 (Nov.–Dec.) 1956.

Because of its potential vasodilating properties, nicotinyl salicylic acid was investigated in the treatment of 22 patients with arteriosclerosis obliterans. The results showed the drug to be of no therapeutic value in occlusive vascular disease. It had no significant peripheral vascular effects in the lower extremities. Neither were there significant effects related to increased walking ability. There was no change with regard to pedal pulses, and oscillometric readings remained unchanged.

AZIONE SEDATIVA DELLA RESERPINA NELL'ANSIA PREOPERATORIA IN GINECOLOGIA.
(Sedative action of reserpine in preoperative anxiety in gynecology).
Migliavacca, A., and Ferraris, F. *Minerva ginec.* (Italy) **8:** 528, 1956; through *Ciba Lit. Review* **1:** 356 (Dec.) 1956.

The tranquilizing action of Serpasil was used to relieve preoperative anxiety in 50 patients who were to undergo gynecologic operations of various types. In order to avoid suggestion, the patients were not told the purpose of the treatment. On each of the four days preceding the operation, they received 1 mg. of Serpasil in tablet form. All of the patients—even the most anxious and excited ones—became more tranquil as a result of treatment with Serpasil. They showed a tendency to sleep and rest, but did not lose interest in their environment. They awaited the operation quietly and with equanimity. The drug had the advantage of shortening the period of intestinal atonia postoperatively. During Serpasil medication, a close watch was kept on pulse, respiration, body temperature, blood pressure, blood count, and bleeding and coagulation times, but no changes were observed.

THE HEMODYNAMIC CONSEQUENCES OF MYOCARDIAL INFARCTION.
Müller, O., and Rørvik, K. *Acta med. scandinav.* **156:** (Supplement 319): 104–111, 1956.

Catheterization of the heart was performed 18 times in 17 patients with coronary heart disease and electrocardiographic signs of myocardial infarction. The procedure was performed one month after the last infarction in 1 patient and two months thereafter in another. In the remaining patients, it was performed from three months to eight years after infarction. The patients varied in age from 45 to 84 years, 5 being from 50 to 59 years of age, and 9 from 60 to 69 years old. Patients with pain as the principal symptom, and normal heart shadows upon x-ray examination, were found in most cases to have normal hemodynamic findings at rest. Some showed signs of left ventricular failure on exercise, even without subjective dyspnea, whereas others had normal or nearly normal findings during moderate exercise. Patients with dyspnea as the principal symptom and an enlarged heart usually had hemodynamic signs of left ventricular failure at rest that became more pronounced during exercise.

ÉTUDE DE L'ALDOSTÉRONURIE CHEZ LE SUJET NORMAL ET CHEZ LE CARDIAQUE OEDÉMATEUX. II. EFFET DE LA PREDNISONE CHEZ LES CARDIAQUES. (THE STUDY OF ALDOSTERONURIA IN THE NORMAL SUBJECT AND IN THE EDEMATOUS CARDIAC PATIENT. EFFECT OF PREDNISONE IN CARDIAC SUBJECTS).
Muller, A. F.; Manning, E. L., and Riondel, A. M. *Schweiz. med. Wchnschr.* **86:** 1362 (Dec. 1) 1956.

The administration of 20 to 40 mg. of prednisone daily along with Diamox to 2 cardiac patients and 1 patient with cirrhosis of the liver with a fixed amount of salt in their diets,

produced a sodium and water diuresis and a decrease in aldosteronuria. These patients had been edematous and refractory to other treatment. No correlation existed between the rates of excretion of aldosterone and of sodium. The clinical improvement brought about by prednisone did not appear to be due exclusively to its inhibitive action on aldosterone. Prednisone appeared to have a direct effect upon the excretion of sodium and water by augmenting the glomerular filtrate which governs the rate of excretion of endogenous creatinine. The lowering of aldosterone in the urine during the administration of prednisone could be attributed in part to inhibition of ACTH secretion by this hormone and in part to the effect of change in the distribution of water for the benefit of the extracellular spaces. In a fourth patient with congestive heart failure who had been under a regimen of salt restriction for many years and who no longer responded to mercurial diuretics nor to Diamox, it was demonstrated that under the action of prednisone the therapeutic effect of the diuretic substances reappeared. A combination of prednisone and Diamox or prednisone and Thiomerin lowered aldosterone values more than did prednisone alone. When administered alone, these diuretics usually cause an increase in aldosterone in the urine.

THE CORONARY CIRCULATION IN MYOCARDIAL INFARCTION.

Muri, J. W. *Acta med. scandinav.* **156** (Supplement 319): 112–124, 1956.

The rate of obstruction, the efficiency of the collateral circulation, and the localization of the occlusion are of major importance in the prognosis of coronary artery disease. Therefore, the relation to major branches should be recorded rather than the distance measured in centimeters from the point of emergency. This is especially important with regard to the left descendent artery, the artery which is most frequently the site of occlusive lesions. Whereas old occlusions are common in the distal segment and rarely cause much damage to the myocardium, old occlusions in the first part of this artery are relatively infrequent and often associated with extensive scars in the ventricular wall. Fresh thrombosis of the first part is a common cause of death in coronary heart disease. (Author's conclusion and summary.)

LONG TERM PROGNOSIS OF MYOCARDIAL INFARCTION. ANALYSIS IN RELATION TO RUSSEK'S CLASSIFICATION OF "GOOD" AND "POOR" RISK CASES.

Olsen, O. C.; Kahrs, T.; Rømcke, O., and Lingjaerde, P. *Acta med. scandinav.* **156:** Supplement 319, 17–26, 1956

This is a follow-up study of 239 patients seen during the years 1936 through 1951 after a first myocardial infarction which was verified in every case. The patients were divided into good-risk and poor-risk groups according to the classification of Russek and his coworkers. An attempt was made to determine which patients might be considered in need of continuous treatment. One hundred and thirteen patients died in the hospital or within two months, so that there were 126 who could be followed. No patient received treatment after discharge from the hospital, but during the years 1947 to 1951 most of the patients received anticoagulant drugs during their hospital stay, or for about four weeks. At the end of the observation period, 39 patients were still alive, and 87 had died. Among these 126 patients, 86 were classified as good risks and 40 were regarded as poor risks. Fifty-eight (46 per cent) died within five years; 68 (54 per cent) lived longer than five years, and of these, 22 patients (17.8 per cent) lived more than ten years. Ten in the last group are still alive. The number surviving longer than ten years may increase, inasmuch as some the remaining 29 living patients may also survive longer than ten years. The causes of death in the 87 patients who died were as follows: probable new infarction, 27; sudden death, 15; congestive heart failure, 18; cerebral hemorrhage, 7; carcinoma, 3; other diagnosis, 7; and unknown or doubtful diagnosis, 10. The mean age of the patients in this study was somewhat higher than in many other reports. Forty-eight patients between the ages of 60 and 69 years, who formed the largest age group by decades, had survival rates among those classified as good risks as follows: two months to five years, 33 per cent; five to ten years,

27 per cent; over ten years, 15 per cent; and among the poor-risk patients, respectively, 15 per cent, 8 per cent, and 2 per cent. Good-risk patients were found to live longer than poor-risk patients, but they died of a new infarction just as frequently. Among 22 patients living more than ten years, only 3 were classified as poor risks. The mean length of life of 86 good-risk patients was 73.2 months and the corresponding figure for the poor-risk patients was 43.2 months. Among 87 patients who died later than two months after acute infarction, 42 died of a probable new infarction or died suddenly. Among these 42, 31 patients belonged to the good-risk group. It is concluded from this finding that, if the aim of long-term anticoagulant therapy is to prevent the development of a new infarction, then patients considered to be good risks should have the benefit of such treatment. Paradoxically, good-risk patients should be treated with anticoagulant drugs prior to patients in the poor-risk group because a relatively high number of the latter die of congestive heart failure.

LES MÉDICATIONS ANTI-INFLAMMATOIRES DANS LE TRAITEMENT DE LA TUBERCULOSE MÉNINGÉE, PLEURALE ET PULMONAIRE. INDICATIONS. (ANTI-INFLAMMATORY DRUGS IN THE TREATMENT OF TUBERCULAR MENINGITIS, PLEURAL AND PULMONARY. INDICATIONS).

Paraf, J., and Paraf, M. *Sem. hôp. Paris* **32:** 2499, 1956; through *Ciba Lit. Review* **1:** 344 (Dec.) 1956.

The anti-inflammatory action of ACTH and adrenocortical hormones can be utilized in the treatment of certain tubercular affections. In severe cases of tubercular meningitis or in those resistant to antibiotics, for instance, these hormones can bring about a decisive turn for the better. Antibiotic therapy, however, should always be continued. Hormone treatment is particularly indicated in the case of infants, in the presence of concomitant miliary tuberculosis, and in any form of the disease that takes a severe course. ACTH is administered by drip infusion in a dosage of 12 to 15 mg. daily for about a week; after a pause of five or six days, a new course of treatment can be started. Prednisone has also proved useful in these indications. In especially severe cases, when the cerebrospinal fluid has a high protein content, 0.5 to 1 cc. of hydrocortisone is injected daily by the intralumbar route. These hormones may be expected to produce rapid results in 40 to 50 per cent of cases of pleural tuberculosis. Their effect in other forms of the disease becomes apparent only gradually. Hormone therapy is always indicated in acute cases. Hydrocortisone (80–100 mg.) —or better still, prednisone (80 mg.)—is administered daily for two to three weeks in addition to tuberculostatic agents. If necessary, a new cycle of treatment may be begun after an interval of fourteen to twenty days.

CORTISONE E CORTISONICI NEL TRATTAMENTO DELLA MENINGITE TUBERCOLARE (CORTISONE AND RELATED SUBSTANCES IN THE TREATMENT OF TUBERCULAR MENINGITIS).

Santopadre I., and Silanos, G. *Minerva med.* **47** (II)**:** 468, 1956; through *Ciba Lit. Review* **1:** 343 (Dec.) 1956.

Glucocorticoids and tuberculostatic agents in combination produced good results in tubercular meningitis. The daily dosages of cortisone were, initially, 100 mg. for adults, 50 mg. for children, and 15 to 20 mg. for infants. The corresponding amounts of prednisone or prednisolone were 30 mg., 15 mg., and 10 to 15 mg., respectively. The dosage of each was gradually reduced during the course of treatment, which usually lasted for twenty to twenty-five days. The hormone rapidly brought about considerable improvement in the general state of health, the improvement being especially marked in comatose patients. The body temperature and neurologic findings were favorably influenced. The optic nerve, in particular, seemed to be affected less frequently and less severely. The rise in intracranial pressure was not so pronounced and examination of the cerebrospinal fluid showed

improved findings. It may be assumed that hormone therapy tends to prevent blocking of the spinal canal or of the cisternae. When this complication has already occurred, intralumbar or intracisternal injection of hydrocortisone elicits a good response. The hormones caused no side-effects. Isoniazid and streptomycin were better tolerated as a result of their administration.

LECZENIE DUSZNICY BOLESNEJ RESERPINA (THE TREATMENT OF ANGINA PECTORIS WITH RESERPINE).

Szajna, M. *Przegl. lek.* (Poland) **12** (II): 186, 1956; through *Ciba Lit. Review* **1:** 358 (Dec.) 1956.

The author first noted the good effect of Serpasil when he used it in a patient who had had a myocardial infarction three years previously and had returned to the hospital every few months because of intolerable pain in the region of the heart and in the left hand. This was a typical case of angina pectoris unaccompanied by signs of myocardial insufficiency. In response to Serpasil (0.25 mg. four times daily), the pains disappeared after twenty days. Despite the brief duration of therapy, no further attacks of angina pectoris have occurred for a year. Similar treatment was used in 9 other patients with coronary artery disease whose ages ranged from 50 to 70 years. In some of these patients, myocardial damage without circulatory decompensation was present. Serpasil (1 to 1.5 mg. daily for fourteen to twenty-five days) prevented pain and improved the general state of health of every patient. No relapse occurred within six to twelve months after treatment was discontinued. It is concluded that Serpasil is of value in the treatment of angina pectoris.